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Studies in Peripheral Arterial Occlusive Disease

I. Methods and Pathologic Findings in Amputated Limbs

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A new technic is described for the study of the arterial circulation of amputated extremities. The method is based on the use of a radiopaque injection mass containing lead and gelatin, and a procedure for unrolling the extremity so that the major arteries lay in one plane. Data are presented concerning the extent and location of arterial occlusion, narrowing, calcification and interarterial anastomosis in 66 legs amputated because of arteriosclerotic gangrene.

DESPITE the clinical importance and the intense interest in arterial disease of the lower extremities, knowledge of the extent of the lesions and of the anastomotic circulation in the normal and in various disease states is incomplete. Although it is generally recognized that anastomoses exist, their extent, their size, their normal functional significance and the derangements that may occur in disease have not been adequately studied. The situation is seemingly analogous to that which existed regarding the coronary circulation before studies by various investigators were undertaken in the last decade. It has been the purpose of this investigation to bridge some of these gaps in our knowledge by clarifying the relationship of the pathologic changes in the arteries, and other tissues of the extremities, to the clinical manifestations of arterial insufficiency.

This initial report describes a method for the arterial injection and dissection of human legs that were obtained subsequent to surgical amputation. It includes data relative to arterial narrowing, occlusion, and calcification, and their relation to interarterial anastomosis and gangrene. In addition, some of the clinical implications of these observations are discussed.

LITERATURE

Shortly after the introduction of the roentgen ray, vascular structures of the human body were injected with radiopaque substances and visualized on x-ray film.[1] Before the turn of the century calcification of the peripheral arteries in man had been noted on the roentgenogram.[2] Despite these early observations, there have been relatively few postmortem studies of the peripheral arteries utilizing radiopaque media. The paucity of these observations is in sharp contrast to the extensive literature relating to arteriography of the vessels of the lower extremities during life.

In 1924 McKittrick and Root[3] injected the arteries of 15 amputated extremities with a fine suspension of barium sulfate and x-rayed and dissected the specimens. They noted the extent of the col-

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lateral circulation as visualized on the roentgenogram and suggested that there was a correlation between collateral circulation and the extent of gangrene. Horton in 1930,[4] using metallic mercury, injected the arteries of 42 amputated extremities and dissected the vessels with the roentgenogram as a guide. He concluded that "the older the person, the less adequate the collateral circulation," and emphasized that there was no way clinically to distinguish between patients who at amputation were found to have widely differing amounts of arterial obstruction. In 1934, Belou[5] injected more than 400 human legs with a variety of radiopaque substances. He was, however, primarily interested in normal anatomic relationships. In 1950, Lindbom[6] injected, x-rayed, and dissected the lower extremities in 186 cadavers. He used a gelatin-acacia-barium sulfate mixture. The principal object of this investigation was to study the roentgen localization of arterial thrombosis in the large arteries of the leg.

In all the papers mentioned, interest was focused principally on the main vessels and to a lesser degree on the collateral circulation. Little information was reported concerning pathology in the branches of the major arteries. The extent of the collateral circulation was estimated from the roentgenogram but scant data on the size or location of anastomotic channels was recorded.

Methods

A. Technic of Injection and Dissection

The development in this laboratory of a technic for injecting and dissecting the coronary arteries,[7] and its use in the study of coronary heart disease,[8] suggested that a similar method might be profitably employed in the study of the arteries of the legs. Contributing significantly to the success of the coronary artery injections were the nature of the standard injection mixture and the method of unrolling the heart so that the coronary arteries lay in one plane.

The lead-agar mass employed so effectively for injection of the coronary arteries required that the heart be immersed in a water bath until the temperature of the entire specimen was at 44 C. Such a procedure was attempted and a small series of amputated extremities were injected with this mass.[9] The method was, however, technically awkward, and the results less reliable than those obtained in the heart. During the course of this preliminary work a technic was devised for unrolling the leg so that its main arteries all lay in one plane. It remained to develop an injection mass having the desirable properties of the lead-agar mixture without the necessity of warming the extremity to 44 C.

1. *Injection Mass.* (a) *Properties of Mass.* It was felt that, in addition to being fluid at temperatures ranging from 0 C. to 20 C. so that the specimen need not be warmed, the ideal injection mass should satisfy the following criteria: (1) it must not be injurious to tissues; (2) it must have sufficient radiopacity to allow visualization of small vessels; (3) it should penetrate to all the smallest arterioles but not enter the capillary bed or beyond; (4) it should remain entirely within the vascular tree; (5) it should be of such a nature that the injection may be completed rapidly; (6) it should be possible to harden the mass permanently and rapidly after injecting it, so that none could escape during the unrolling process; (7) it should be flexible enough, after hardening, so that the leg could be unrolled without distortion; (8) it should contain no large particles, to obviate the danger of producing factitious occlusions; (9) it should be readily removable during the dissection of the arteries; and finally, (10) it should not interfere with the preparation of microscopic sections if left in the injected specimen. Several masses employing latex or various plastics as a base were considered but none was found to be suitable. A mass utilizing lead and gelatin in appropriate proportions met all of the criteria just listed except that it required two and one-half hours to harden and on rare occasions went across to the veins.

The lead-gelatin mass is a creamy, white suspension containing 15 per cent of lead and 10 per cent of gelatin. The insoluble lead phosphate falls out of suspension so slowly as not to interfere with the injection procedure. The pH of the mass after paraformaldehyde has been added is 6.3. Relative to distilled water at 25.5 C. and 400 mm. Hg pressure, and tested on the same viscosimeter, the mass after the setting agent, paraformaldehyde, has been added has an initial viscosity of 11. The viscosity of the mixture gradually increases after the setting agent is added. The mass remains relatively fluid for 30 minutes, doubles its viscosity in 90 minutes and becomes solid in two and one-half hours.

Although the viscosity is definitely a function of time and of temperature, neither of these factors has affected the setting time sufficient to interfere with the injection of amputated extremities. Mass that has been stored at room temperature for as long as two months before adding the setting agent has been entirely satisfactory.

The level of penetration of the lead-gelatin mixture evidently depends on many properties in addition to the size of the individual particles. Most of the particles of lead phosphate are less than 3 micra in diameter, yet the mass does not penetrate vessels many times larger. Small variations in the herein described method of preparation of the mass or of the technic of injection apparently cause wide differences in the extent of penetration. These differences range from "stumpy" injections of only the larger arterioles to very "fine" injections with filling of many unusually small arterioles. Over a 12-

month period, however, only two preparations of mass penetrated to the venous circulation.

The mass was regularly found in vessels 60 micra in internal diameter, irregularly penetrated as far as vessels from 60 to 12 micra in diameter, but was not found in vessels under 12 micra in diameter. These measurements of vessel size were made on stained microscopic sections prepared from tissue fixed in formalin and embedded in paraffin; they are, therefore, subject to a correction of about 50 to 100 per cent for shrinkage from the fresh unfixed state.

b) *Preparation of Mass*

Stock Solutions

(1) 88 per cent phenol (acid carbolic, liquified).

(2) 0.3 per cent phenol red (water soluble).

(3) 1 molar lead acetate (Pb $(CH_3COO)_2 \cdot 3H_2O$) C.P.

Caution: do not allow lead acetate crystals or solution to remain exposed to air.

(4) 1 molar potassium acid phosphate (KH_2PO_4) C.P.

(5) 1 molar potassium alkaline phosphate (K_2HPO_4) C.P.

Caution: add 2 cc. 88 per cent phenol (solution 1) per liter potassium alkaline phosphate to prevent mold growth.

(6) 6 per cent paraformaldehyde (trioxymethyline)

140 cc. distilled water
0.7 cc. 0.3 per cent phenol red (solution 2)
0.6 cc. 1 molar potassium alkaline phosphate (solution 5)
12 grams paraformaldehyde

Heat to vigorous boil in 500 cc. Erlenmeyer flask with vented stopper; when color turns yellow, allow to cool, filter, bring volume to 200 cc. and store.

(7) 1 per cent watery solution fast green

Lead Phosphate Precipitate (*Mixture A*)

Prepare eight 2500 cc. reagent bottles in the following manner:

100 cc. 1 molar lead acetate (solution 3), 75 cc. 1 molar potassium alkaline phosphate (solution 5). Shake well, bring to 2400 cc. with tap water, shake well; after precipitate settles, suction off supernatant to 400 cc. mark. Repeat procedure of filling with tap water to 2400 cc. mark and suction off to 400 cc. mark six times in each bottle.

Divide contents of eight bottles equally between two 2000 cc. graduates. After precipitates settle, suction off supernatant to 800 cc. mark in each graduate.

Gelatin-Potassium Iodide Mixture (*Mixture B*)

Thoroughly mix 200 Gm. Difco Bacto gelatin and 300 Gm. granular potassium iodide (KI) C.P.

100 cc. 1 molar potassium alkaline phosphate (solution 5); 75 cc. 1 molar potassium acid phosphate (solution 4). Dilute to 1000 cc. with distilled water; heat 750 cc. of above mixture to 70 to 80 C. in pyrex dish; remove from heat and stir with power mixer; add 8 cc. 88 per cent phenol (solution 1); add gelatin-potassium iodide mixture (500 Gm.); continue stirring (for at least two hours) until all particles dissolve.

Lead-Gelatin Mixture

800 cc. mixture A; 800 cc. mixture B; mix well; allow to settle; suction off supernatant to 1000 cc. mark, filter through 44 micro sieve and store.

2. *Injection Procedure.* Lateral and anteroposterior roentgenograms of the amputated leg were made before injection. The extremity was suspended in the upright position by inserting No. 22 copper wire through a hole drilled through the most proximal cut end of bone. A flanged glass cannula was secured within the popliteal artery with size 0 surgical silk.*

Just prior to injection 2 cc. of 1 per cent fast green (solution 7) and 10 cc. of 6 per cent paraformaldehyde (solution 6) were added to 100 cc. of the lead-gelatin mass and shaken vigorously in a glass stoppered graduate. To this mixture 3 drops of caprylic alcohol were added to remove air bubbles from the mixture. The graduate containing the mass was immediately attached both to the arterial cannula and a mercury manometer which was so connected that a source of constant pressure of 400 mm. Hg could be imparted to the system.

On completion of the injection, lateral and anteroposterior roentgenograms were again obtained. The specimen was then placed in the refrigerator for two hours by which time the mass in the arteries was solid. The limb was unrolled according to the procedure described below and additional roentgenograms taken. The x-ray factors employed were as follows: for intact extremities 15 ma., 55KV, 1.25 to 1.50 second, 48 inches (tube to film); for unrolled specimens 15 ma., 48KV, 0.50 to 0.75 second, 48 inches (tube to film).

The lead-gelatin mass was injected at a pressure of 400 mm. Hg. This pressure was chosen because at 200 mm. Hg, injection of the toes often was incomplete. Pressures higher than 600 mm. Hg often caused rupture of arteries and extravasation of mass.[10] Furthermore, 400 mm. Hg pressure did not result in intimal tears, dislocation of thrombi, vascular rupture, or extravasation.

During injection, mass invariably leaked at the cut edges from vessels severed at the amputation

* In several of the lower leg amputations, two or three of the principal arteries were cannulated separately. This permitted multiple color injections.

level. These leaks could be partially controlled with hemostats. The injection was permitted to continue until no more mass entered the leg or leaked from vessels at the cut edges of the leg. This required about 30 minutes by which time the mass in the graduate had become very viscous although not so solid that it would not flow.

3. *Method of Unrolling the Leg.* A method of unrolling the leg was devised so that the major vessels would lay in as close to one plane as possible and so that the dorsal and plantar arches of the foot could be separated. In addition, some of the bones in the leg had to be removed so that they would not unduly obscure the arterial shadows. The steps of this unrolling procedure follow.

STEP 1. A single incision was made through the skin and carried down to the underlying bones. This incision coursed along the anterior aspect of the leg from the cut end of the femur to the ankle. There it turned medially, anterior to the medial malleolus, and passed along the medial aspect of the foot to the first metatarsal phalangeal joint. At this point it turned dorsally crossing the dorsum of the foot at the metatarsal-phalangeal joints. The incision ended at the lateral aspect of the fifth metatarsal phalangeal joint (fig. 1A).

STEP 2. The femur was cleared of surrounding soft tissues, disarticulated from the tibia, fibula and patella, and removed from the specimen. The patella was left in situ. The tibia was then cleared of surrounding soft tissues, disarticulated from the fibula at the knee and the fibula and talus at the ankle, and removed from the specimen (fig. 1B). The fibula was left in situ.

STEP 3. To facilitate the separation of the dorsal and plantar arches, the talus was disarticulated and removed from the specimen (fig. 1C).

STEP 4. The five metatarsal phalangeal joints were disarticulated, and then dissected from the soft tissues on the sole of the foot. Using the soft tissues lateral to the fifth metatarsal phalangeal joint as a pivot, the metatarsal bones were extended laterally with the soft tissues of the dorsal aspect of the foot (fig. 1D).

The fibula was left undisturbed in order to provide a rigid support to the specimen and preserve the constancy of the anatomic relationships. Removal of bones in the foot, other than the talus, added little to the roentgenologic visualization of the arteries and caused additional fracture of important vessels.

4. *Dissection Technics.* Using the film of the unrolled leg as a guide, almost all vessels 1 mm. or larger were dissected. Selected labeled sections of artery, vein, nerve, muscle, and skin were taken for microscopic examination. Arteries containing calcium were decalcified by the method of Foord[11] after being fixed in formalin.

During dissection the nature and location of the arterial pathology as well as the extent of the dissectible and nondissectible interarterial anastomoses and of necrosis were carefully determined and compared with the roentgenogram. This data was preserved for subsequent study by transfer, at the time of the dissection, to tracing paper overlying the roentgenogram. Fluid blood or postmortem clots were occasionally found in the arteries. Although these artefacts could simulate arterial occlusion or narrowing on the film of the injected leg, they were easily recognized at the time of dissection.

B. Criteria for Occlusion, Narrowing, Calcification, and Anastomosis

The technic employed disclosed the occlusions, narrowings, vascular calcifications and interarterial anastomoses in the visualized arteries in each leg.

1. *Occlusion.* Although areas of occlusion and narrowing stood out on the film as irregularities in the shadow of the injected mass, the presence, degree, and age of the arterial occlusions and narrowings were decided finally during the arterial dissection. Except where segments were taken for microscopy, all injected arteries were routinely opened down to small branches. Solidified mass was found in them as a cast of the size and shape of the lumen. This facilitated determination of the presence of complete occlusion or the degree of narrowing. The staining of the intima by dye diffused from the mass also aided dissection of small or narrowed vessels. At sites of occlusion, a complete break in the continuity of the lumen was demonstrated when neither mass nor stained intima was observed at the time of the dissection. Occlusions were further classified as fresh or old on the basis of their gross appearance. Microscopic studies of many areas of occlusion were made for more accurate estimation of the duration and nature of the occlusive process. The term "occlusion" as used in this communication always denotes complete occlusion.

2. *Narrowing.* The degree of narrowing for each narrowed segment in the arteries of each leg was classified as slight, moderate, or marked. Small, intimal atheromas without any grossly distinct narrowing of the lumen were placed in the normal group without narrowing. "Slight narrowing" referred to vessel segments with slight but definite constriction of the lumen; "marked narrowing" signified unequivocal, extreme reduction in the arterial lumen; "moderate narrowing" included all vessel segments with intermediate degrees of obstruction. In several extremities the diameters of the major vessels were measured from the roentgenograms, so that the percentage reduction in diameter at areas of narrowing in comparison with immediately adjacent zones was quantitatively determined. Qualitative estimates of slight narrowing were found to correspond approximately with a reduction in diameter of 25 per cent or less; marked narrowing was equivalent to 75 per cent reduction

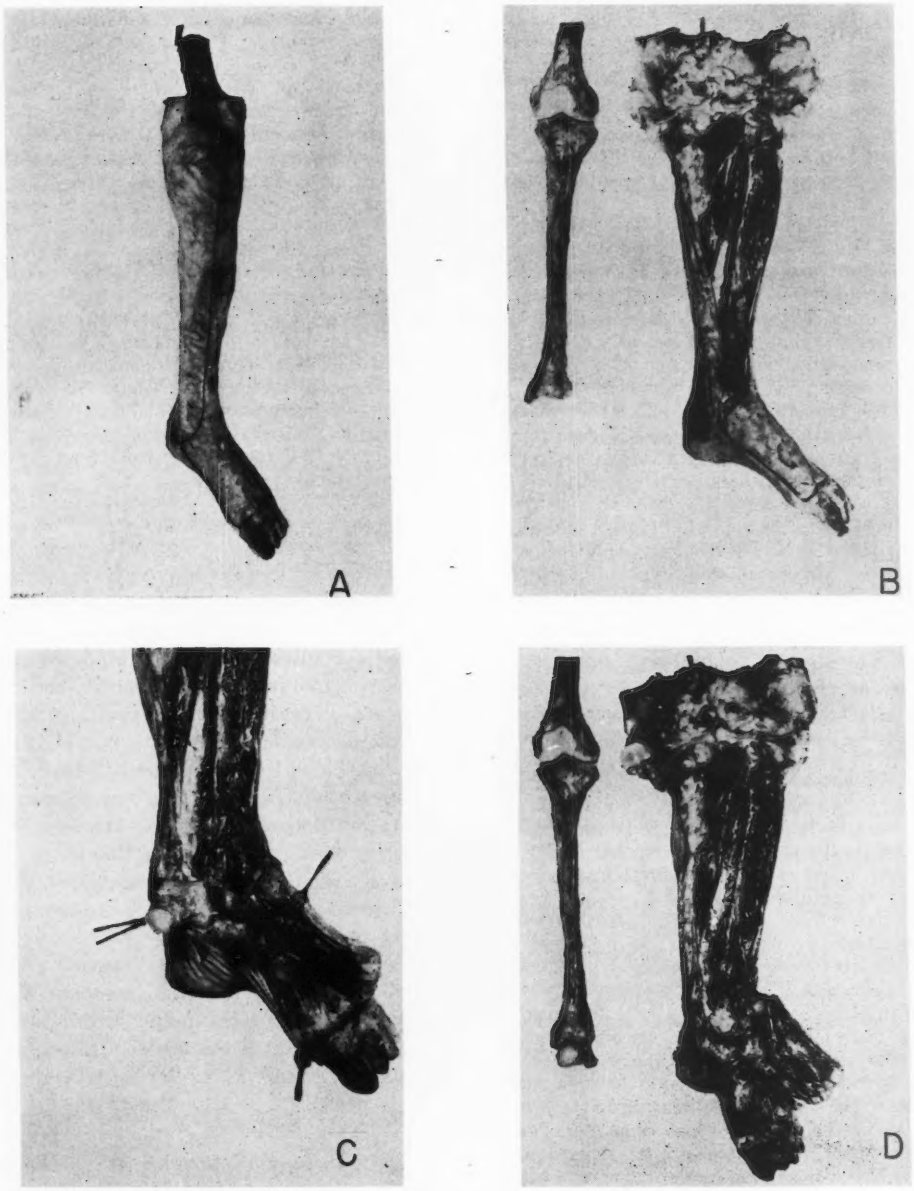

FIG. 1. Unrolling procedure. (*A*) Step 1: line of incision. (*B*) Step 2: removal of femur and tibia. (*C*) Step 3: removal of talus. (*D*) Step 4: separation of dorsal and plantar arches of foot.

more. Narrowings were further classified as fresh old on the basis of their gross appearance.

3. *Calcification.* The extent of arterial calcification could in large part be determined from the roentgenograms taken before and after injection and from the arterial dissection. The relation of such calcification to the various elements composing the arterial wall was often difficult to determine from the films or at the time of arterial dissection. This was particularly true when, as so often hap-

pened, both intimal and medial calcification were present in the same zone. Indeed, such a distinction in some of these sites was often difficult in the microscopic sections.

4. *Interarterial Anastomosis.* It was found that the roentgenogram alone, even of the unrolled leg, could not be relied upon to prove the existence of anastomotic communications. Overlapping vessels often misleadingly appeared on the film to intercommunicate. Conversely, anastomoses later clearly demonstrated on careful dissection were not traceable on the roentgenogram because of extensive overlapping of injected vessels. On the basis of careful dissection three types of proof were accepted: (1) demonstration, after opening, of a continuous, intact, endothelial-lined small channel filled with mass connecting two larger arteries, or demonstration of an absolutely continuous, intact, distinct vessel with a diameter too small to be opened in its entirety but which was shown at both ends to connect with larger opened endothelial-lined channels; (2) presence of injection mass distal to a complete occlusion; (3) visualization of a mixture of color in the injection mass. In the first instance the pathway was dissectible, in the latter two instances the demonstration of a dissectible pathway was not essential.

Grossly dissectible anastomoses were demonstrated only when the vessel exceeded 0.2 mm. in diameter, which also was the smallest vessel regularly visualized on the roentgenogram. Although some anastomoses 60 to 70 microns in diameter could be traced along their entire course with the aid of the dissecting microscope, they were not routinely looked for in this study.

The second criterion for interarterial anastomosis depended on the presence of a complete occlusion. Since such a lesion prevented direct filling of the vascular tree peripheral to it and since the mass did not ordinarily reach capillaries or veins, or escape from the vascular tree, mass found beyond an occlusion must have arrived there via collateral arterial pathways.

The third criterion for interarterial anastomoses depended on a mixture of color in the injected mass. In those legs in which the popliteal artery was completely occluded, or in which a lower leg amputation had been performed, more than one artery was cannulated and differently colored masses were used in each cannula. Since the color of the injected mass identified its source, a mixture of colors necessarily indicated a connecting pathway between the two separately injected arteries.

Material

A total of 72 amputated lower extremities were studied; 37 of these were amputated at the Beth Israel Hospital, and 35 at the Boston City Hospital.* The etiologic factors responsible for amputation are indicated in table 1.† These included arteriosclerosis (66 cases), embolism (3 cases), osteomyelitis (2 cases) and sarcoma (1 case). There were no cases of thromboangiitis obliterans. In 11 of the 72 legs the occlusive process in the large arteries near the amputation site was so extensive that no vessels suitable for injection could be found. These extremities were dissected without injection and although no data in them was available concerning interarterial anastomoses, information on occlusions in the main stems was utilized. In five of the legs the major vessels after being injected and x-rayed were dissected from the remainder of the extremity. These vessels were fixed in toto, decalcified, again x-rayed and selected sections taken for microscopic study. By this special study certain details concerning the branches of the main vessels and some information relating to collateral circulation were sacrificed. However, such data as was available from these five legs was also used.

Results

A. Arterial Anomalies

The configuration of the major arteries of the lower leg was relatively constant although minor anomalies were present in 15 per cent of the 72 extremities. Four distinct variations were noted. In six legs the peroneal artery was absent; in three limbs the anterior tibial artery did not extend to the ankle, the dorsalis pedis being formed in each instance from the peroneal artery; in one extremity the posterior tibial artery was absent, and in another leg it arose from the popliteal, above the origin of the anterior tibial. In no extremity did more than one of these anomalies occur. All of the variations could be readily seen on the films of the unrolled leg. The relative constancy of the arterial pattern of the major arteries of the lower leg facilitated the use of the roentgenograms in this study.

B. Arterial Occlusion

For the study of arteriosclerosis the legs amputated for arterial embolism (cases 21, 35, 64), for osteomyelitis (cases 28, 70), and for sarcoma (case 16) were not used. This left 66

* The legs from the Boston City Hospital were made available through the courtesy of Dr. Frederick Parker, Jr. and his associates at the Mallory Institute of Pathology.

† At the request of the Editor all tables are being omitted. These will be furnished on request.

legs in which arteriosclerosis and gangrene were sufficiently severe to necessitate amputation. Fifty-two of these were low thigh amputations and 14 were removed below the knee (table 2).* Because of congenital anomalies and the varying level of amputation there were 244 major arteries (popliteal, anterior tibial, posterior tibial and peroneal) available for study (table 3).*

1. Incidence of Occlusions. (a) *Main Vessels.* Extensive occlusive disease was present in the major arteries. In each amputated limb at least one point of complete occlusion was found; in 91 per cent of the extremities two or more of the four major vessels were completely occluded, usually at more than one site. The frequency of occlusions of each of the four major vessels is indicated in table 3*. Among the 46 injected low thigh amputations in which complete observations were possible there were 398 old and fresh occlusions—an average of more than eight sites of complete occlusion per leg (figs. 2 and 3).

The extent of the arterial occlusive disease was also evaluated by determining relative lengths of the vessels occluded rather than the number of occlusions per leg or the number of major vessels involved. In 51 amputations in which injections of the major arteries were successfully carried out, accurate measurements of the entire vessel lengths of the arteries of the lower leg and of the lengths occluded were made from the roentgenograms at the time of dissection. Twenty-six per cent of the total length of these four major arteries were completely occluded (table 4).*

(b) *Branches.* Occlusions in primary branches of the four main arteries 1 mm. or more in diameter were found in 56 per cent of the extremities. The incidence of occlusions in the branches was appreciably less than in the main stems and they were, on the average, shorter than those in the major arteries. Although fewer occlusions were present in the main popliteal artery than in the other main vessels, the incidence of occlusions in its branches was significantly greater than that in all the branches of the other three major vessels combined (table 5).*

With the method used, the terminal branches of the anterior and posterior tibial arteries in the foot were readily visualized on the x-ray film but very difficult to follow and dissect. Only a few such detailed dissections in comparison with the accompanying roentgenograms were carried out. These dissections together with careful study of the roentgenograms in the other legs showed very few occlusions in the smaller arterial branches in the nongangrenous portions of the foot and toes, although various degrees of narrowing did occur.

2. Localization of Occlusive Disease. In five legs in which the entire lengths of the tibial arteries were available, only one of the three main arteries in the lower leg was occluded (cases 39, 54, 65, 68, 69). In all five instances the occlusions were in the posterior tibial artery. The length of the occlusions varied from 0.4 cm. (case 54) to 21 cm. (case 39).

There were 12 legs (cases 5, 19, 32, 44, 45, 46, 51, 52, 53, 57, 60, 72) in which only two of the three main arteries to the lower leg were occluded. In all 12 of these extremities the posterior tibial was one of the two vessels occluded; the occlusions ranged from 0.5 cm. to 34 cm. in length. It would appear from these observations that the posterior tibial artery is truly the "artery of occlusion" in the leg. Not only is it the most frequently (table 3)* and most extensively (table 4)* occluded of the tibial vessels, but it is also the first to become completely obstructed by the arteriosclerotic process.

In seven patients both legs were available for injection as a result of bilateral low thigh amputations. Extensive occlusive disease was present in each pair of extremities. In only one patient, however, was the extent of the occlusive disease markedly different in the right and left extremities (table 6)*.

Although 91 per cent of the legs had two or all three major arteries of the lower leg occluded by either fresh or old occlusion, there were a few extremities in which one or two of the four major vessels showed absolutely no atherosclerosis. In one leg (case 50) with multiple occlusions in both the posterior tibial and popliteal arteries and several sites of narrowing in the peroneal artery, the anterior

* See footnote† on p. 646.

tibial artery throughout its length was without an atheromatous plaque. In another leg (case 67) there was extensive occlusive disease of the anterior tibial, posterior tibial, and popliteal arteries, with the peroneal artery entirely free of atherosclerosis.

There was an equal amount of occlusive disease in the major arteries in the proximal, middle and distal thirds of the lower legs whether the amount of occlusive disease was small or large.

3. Fresh Occlusions. Fresh, completely occluding thrombi were present in 46 per cent of the extremities. The distribution among the major vessels is indicated in table 7*. Fresh occlusions were present in 17 per cent of 52 popliteal arteries examined, in 17 per cent of 66 anterior tibial arteries, in 22 per cent of 65 posterior tibial arteries and in 15 per cent of 61 peroneal arteries examined. Similar fresh occlusions were present in four legs in branches of the popliteal artery and in another leg in a branch of the peroneal artery. Although most of the fresh occlusions were about 1 cm. long, they varied from 0.2 cm. to 13 cm.

Fresh occlusions frequently were multiple in the same artery or present in more than one vessel. Half of the extremities with fresh occlusions had two or more such occlusions. All but four of the 71 fresh occlusions were in vessels in which old occlusions were already present; three-fourths of them were distal and one-fourth proximal to the old occlusions. Each fresh occlusion was attached to the adjacent arterial wall at a site of previous narrowing.

In one-third of the extremities there were one or more recent narrowings caused by mural thrombi. These nonoccluding thrombi were always superimposed on sites of old arteriosclerotic narrowing. The injection procedure itself apparently did not dislodge any of these mural thrombi, for free unattached thrombi were never found during the dissection.

C. Arterial Narrowing

In the presence of such extensive old and fresh occlusive disease the functional role of arterial narrowing was difficult to assess. It was clear that as the amount of occlusive disease increased not only the extent but also the degree of narrowing increased. Thus, in legs with occlusions limited to one artery the amount of slight narrowing exceeded the amount of marked narrowing; in legs with occlusion of all three lower leg arteries, the relative amounts of slight and marked narrowing were reversed. Each extremity amputated because of arteriosclerotic gangrene showed occlusion of at least one major leg artery. It appeared, therefore, that narrowing, in the absence of arterial occlusion, may not sufficiently compromise the circulation to produce gangrene.

Areas of narrowing often served as a nidus for the development of fresh thrombi, many of which went on to complete occlusion. On the other hand grossly dissectible anastomotic channels were frequently found distal to sites of old narrowing. These partial obstructions apparently were a stimulus to the development of collateral channels which protected the leg against the sequelae of complete arterial obstruction.

D. Arterial Calcification

In 19 amputated legs preinjection roentgenograms showed arterial calcification in one to four major arteries. The lengths in centimeters of calcification of the popliteal, anterior tibial, posterior tibial, and peroneal arteries and their branches visualized on the preinjection roentgenogram were determined with a map measurer. Because we wished to compare it with the calcification often demonstrated during life, only calcification visible before injection and unrolling was utilized for the present analysis. In these 19 legs there were thus visualized 797 cm. of calcified major arteries. Of these 797 cm. only 19 per cent were found after injection and dissection to be completely occluded. The remaining 648 cm. showed either varying degrees of narrowing or normal lumens. An additional 88 cm. of calcified branches were visible before injection. Of these only 1 cm. was demonstrated to be completely occluded after injection and unrolling.

In these same 19 legs, the combined length of the remainder of the anterior tibial, posterio-

* See footnote† on p. 646.

tibial, peroneal, and popliteal arteries totaled 1339 cm. of which 23 per cent were occluded (table 8).* Thus, in these amputated limbs with advanced arteriosclerotic disease and gangrene, the incidence of occlusion was about

E. Interarterial Anastomosis

As stated earlier interarterial anastomoses can be demonstrated in one of three ways: (1) tracing of a grossly dissectible pathway, (2) finding of mass distal to a complete occlusion, and (3) mixing of differently colored masses injected into separate arteries. The unrolling procedure made visible on the roentgenogram many anastomoses that otherwise would not have been suspected. However, the procedure itself destroyed some anastomotic pathways particularly in the foot where the dorsal and ventral arches were separated.

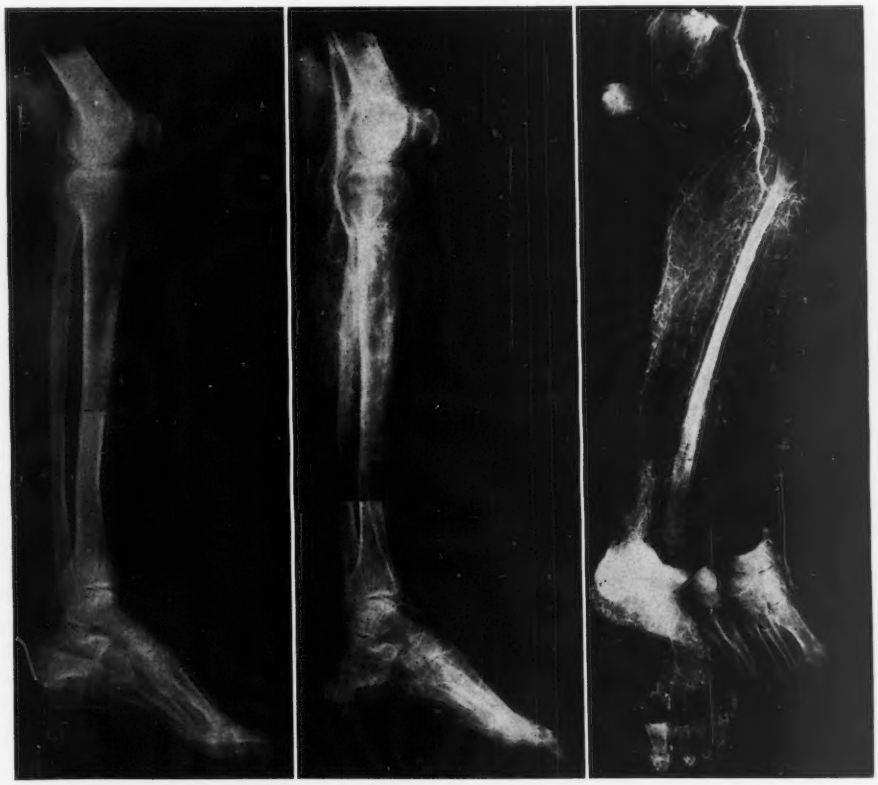

FIG. 2. Roentgenograms and diagrams of amputated leg with multiple arterial occlusions (case 71).

A: Lateral roentgenogram of intact leg prior to injection. Few specks of calcification barely visible along course of anterior tibial artery. *B:* Lateral roentgenogram of intact leg after injection. Extensive occlusions of major vessels and marked small artery injection. *C:* Roentgenogram of leg after unrolling. Eight complete occlusions involving anterior tibial, posterior tibial and peroneal arteries.

the same in vessels in which calcification was not visible on the x-ray film as in roentgenographically visible calcified vessels. This disparity between roentgenologically visible calcification and arterial occlusion is illustrated in figures 2*A*, *B*, *C*, 3 and 4*A*, *B*, *C*.

* See footnote† on p. 646.

Other factors interfering with the dissection and tracing of possible anastomoses included the richness and extensive overlapping of small vessels and presumably collateral blood supply and the devious paths of the small vessels deep within the muscle bundles.

In the arteries of the 56 amputated arteriosclerotic legs successfully cannulated and injected, there were 438 complete occlusions,

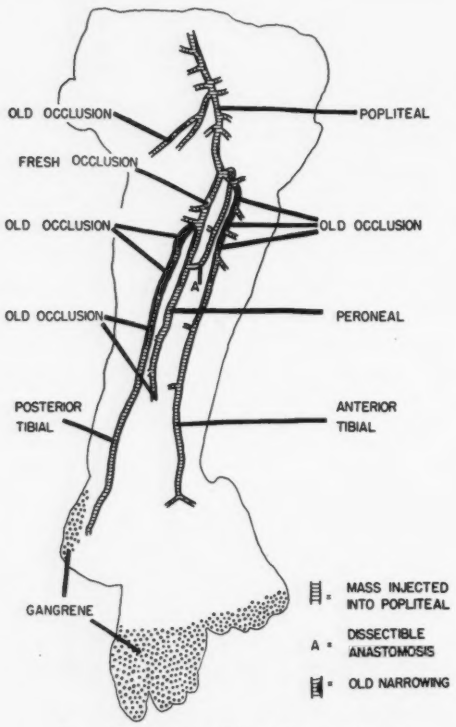

FIG. 3. Diagram of leg after unrolling

some old and some fresh. Except in areas of extensive gangrene, or as a result of technical errors, anastomoses were proved by the finding of injection mass in the occluded vessel distal to all but two of these 438 occlusions. One of these two occlusions was in a branch and the other was a fresh occlusion in a major artery. Injection mass could reach these zones distal to complete occlusions only by anastomotic interarterial pathways most of which were not dissectible.

In 39 extremities grossly dissectible anastomoses were searched for with meticulous care. In 38 of this specially studied group such communications varying in number from 1 to 12 per leg were found (fig. 5*A–B*). In all, 147 such dissectible anastomoses were found in these 38 legs.

Other evidence of collateral circulation was furnished by the leaks from the cut edges at the amputation level. These leaks were multiple, usually could not be completely controlled with hemostats until the mass had become semisolid, and were subsequently shown by roentgenogram and dissection to have come from severed arteries at the amputation site. In the low thigh amputations these leaks signified an anastomotic circulation around the knee joint connecting major vessels of the lower leg with branches of the femoral artery.

In 2 of the 10 injected lower leg amputations it was possible to cannulate more than one major artery and inject each with a differently colored mass. In one lower leg (case 13) two arteries, and in the other (case 16) three arteries were thus injected. In both legs appearance of a mixture of colors distal to several occlusions in all three arteries to the lower leg indicated the richness of the collateral blood supply.

The evidence concerning interarterial anastomoses was amplified in some extremities by additional data of a less conclusive nature than that just presented. In the regions of occluded arterial segments there was frequently on the roentgenogram a diffuse, increased density of negative shadows over what would be found in similar areas with nonoccluded arteries. This increase in density was presumably due to an increased number of small nondissectible arterial shadows. It was not due to grossly extravasated mass. Many of these anastomotic vessels, dissectible and nondissectible, had on the roentgenogram a characteristic corkscrew shape. This has previously been noted during clinical arteriography.[12]

Even in the unrolled leg the richness of the overlapping small vessel injection made it difficult to determine in what plane the anastomoses occurred. In a few legs the skin and subcutaneous tissues were dissected off from the muscles and x-rayed separately. This

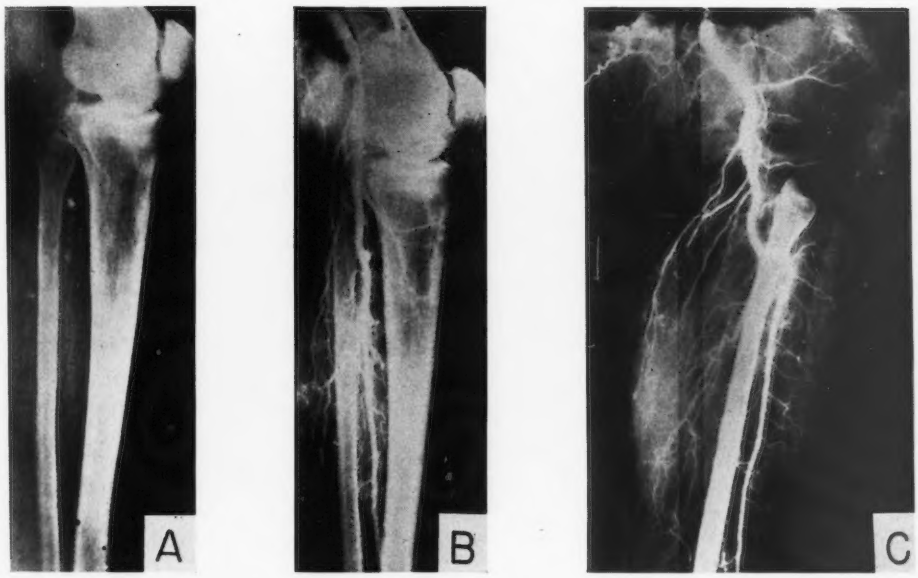

FIG. 4. Roentgenograms of amputated leg showing inverse relation between arterial calcification and occlusion (case 66).

A: Lateral roentgenogram prior to injection. Visible calcification of entire popliteal and anterior tibial arteries and upper fourth of posterior tibial artery. *B:* Lateral roentgenogram after injection. Popliteal, anterior tibial and upper fourth of posterior tibial arteries patent. Occlusion of remainder of posterior tibial and all of peroneal arteries. *C:* Roentgenogram of unrolled leg showing sites of patency and occlusion more clearly than in *B*.

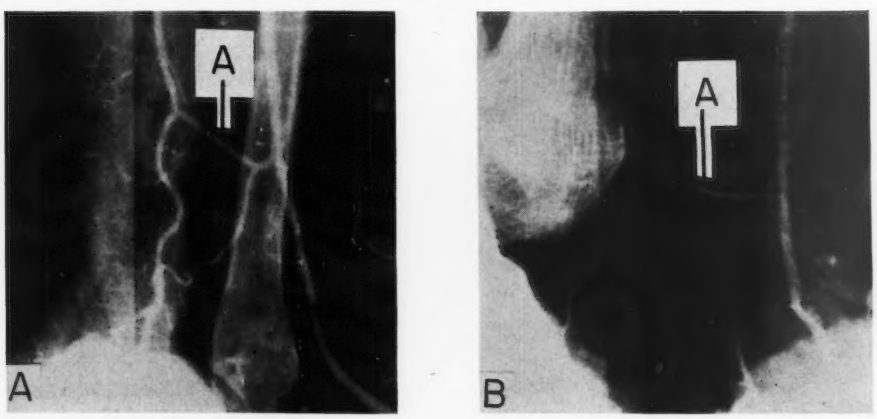

FIG. 5. Roentgenograms of amputated legs after unrolling illustrating size of interarterial anastomoses. *A* indicates anastomotic vessel.

A: Interarterial anastomosis between posterior tibial and peroneal arteries (case 61). *B:* Interarterial anastomosis between peroneal and anterior tibial arteries (case 69).

examination showed that the small arteries in the skin and subcutaneous tissues of patients with extensive occlusions of all three lower leg arteries were very plentiful while the arterial skin circulation in patients with no occlusions or only short occlusions of one tibial artery

was considerably less abundant. Similar results were consistently found in other legs studied in this way.

F. Gangrene

In the total series there was marked variation in the amount of gangrene present and the amount of occlusive disease found in the arteries. The necrosis in each extremity was roughly graded on a scale of one to four, and the amount of occlusive disease similarly graded. Correlation between the amount of gangrene and the extent of occlusion was poor (table 9).* Very minimal gangrene was found with extensive occlusive disease and vice versa.

Discussion

The injection and dissection technic described in this paper has disclosed the number and proportionate lengths of occlusions in the arterial pathways of extremities amputated for arteriosclerotic gangrene. The radiopaque injection mass has such desirable properties that it is being used in this laboratory to examine the arterial circulation of the brain, kidney, and bowel. It holds promise of general use as an adjunct in the study of disease in hollow viscera as well as in the investigation of the blood supply of various organs.

Unpublished injection studies of nongangrenous legs of cadavers indicate that occlusions in the femoral artery are much less frequent than in the main arteries of the lower leg. Lindbom[6] came to similar conclusions. In the arteriosclerotic limb, therefore, the main arteries from the knee to the ankle become the principal bottleneck in the flow of blood from the aorta to the toes. This bottleneck area is most difficult to visualize completely even with a good contrast media. It is much easier both during life and at necropsy to demonstrate the femoral artery, the popliteal artery, or the terminations of the anterior and posterior tibial arteries in the foot than to visualize the tibial arteries in the lower leg. These observations indicate some of the limitations of arteriography of the limb in the living patient. Knowledge of the localization of the occlusive process and the limits of arteriography should temper any surgical plan to relieve the symptoms of vascular insufficiency in the arteriosclerotic limb by restoring the integrity of the arterial lumen in the thigh.[13]

Sappington[14] and others, using unaided dissection of the main arterial stems, have demonstrated that occlusive disease in the leg must be extensive before amputation is necessary. However, there are few published reports estimating the degree of this obstruction in quantitative terms. We have found, in general, that the extent of arterial occlusive disease in the gangrenous leg was of an entirely greater order of magnitude than that found in infarcted hearts studied by a similar technic.[8, 15] Almost no data by a comparable technic is available concerning the degree of arterial obstruction in other viscera. Unaided dissection studies, however, suggest that the extent of occlusive disease in the leg arteries may exceed that of any other segment of the human arterial tree.

An extremely rich interarterial collateral circulation was associated with the extensive arterial obstructive disease found in the leg. Anastomotic channels of sufficient caliber to be grossly dissectible were almost invariably present in these gangrenous extremities. Both the frequency and size of these large channels was of a greater order of magnitude than that found in the heart.[16] Occasionally the internal diameters of these anastomotic leg vessels approached those of the original major arteries they connected (fig. 5*A–B*). This observation may explain the return of pulsatile flow to portions of arteries distal to sites of complete occlusion.

Although in almost every case it was quite clear that the dissectible anastomoses were serving as by-passes, circumventing occluded arterial segments, the question of preformed anastomoses was raised by occasional *dissectible* anastomoses which did not appear to by-pass specific arterial obstructions. Among the specimens examined in this study were two legs with nonvascular pathology: one of these was a lower leg amputation (case 16) for a sarcoma of the heel in a 41 year old man; the other a lower leg amputation (case 70) for a chronic osteomyelitis of the foot in a 27 yea

* See footnote† on p. 646.

old woman. Both specimens exhibited entirely normal arteries and, in both, dissectible anastomoses were demonstrated proximal to the sites of pathology. Moreover, three color injections were possible in both of these extremities, and the extensive mixing of colors also indicated the richness of the anastomotic circulation. It must, of course, be recognized that although these two cases approached normal material from the viewpoint of arteriosclerosis, they were not true controls.

Further support for the existence of preformed interarterial anastomoses in the leg was afforded by the injection of the femoral arteries of cadavers free of arterial disease.[10] Injection of these vessels resulted routinely in extensive filling with mass of the arteries of the abdominal wall.

Is this rich anastomotic circulation in the legs preformed or does it develop in response to arterial obstruction? This question can be answered definitively only by subjecting a series of normal extremities to a similar examination. Although final evaluation awaits such a study, if it can be undertaken, we suspect that interarterial communications may exist normally in the human leg. Preformed collateral channels in the normal leg may, for example, explain why arterial embolization to the limbs of young patients with rheumatic heart disease so rarely leads to gangrene. In the lower leg, anastomotic arteries do not, however, present a uniform pattern comparable to the circle of Willis at the base of the brain or the arcuate arteries of the intestine. Although interarterial communications may be present in the normal human leg, arterial occlusion leads to an increase in their number and size: this was demonstrated by the richness of injected vessels as seen on the roentgenogram near sites of obstruction and the increase in the number and the change in the configuration of the skin arteries with increased obstruction. The localization or "tailoring" of anastomoses to circumvent specific occlusions also supports the hypothesis that anastomoses are stimulated by the occlusive process. Most of the occlusive disease in these gangrenous limbs was limited to the major vessels between the knee and the ankle. The commonest site for large grossly dissectible communications was in the region of the ankle joint. This is precisely where they would be most effective.

From these studies it should be clear that arterial obstruction is primarily responsible for the development of gangrene and that the rich collateral circulation compensates in part for the obstruction to arterial flow, thereby permitting the occlusive disease to become extensive before gangrene supervenes. The pathologic substrate of occlusion and anastomosis which in part determines the fate of a limb, should not, however, be thought of as a constant and invariable picture. It is a shifting background in which changes frequently occur quite rapidly. Although there was a parallel increase of narrowing and occlusion, such narrowing did not necessarily or commonly go on progressively and gradually to occlusion. Instead the process was periodically accelerated by the sudden development of complete thrombotic occlusions. Indeed, fresh thrombotic occlusions were found in about half of these legs. Such thrombi were frequently several centimeters in length and often multiple. Although most of them were distal to sites of old occlusions, they still played an important role in diminishing the blood supply to the foot. They often plugged arterial segments which previously functioned as conduits by which blood was passed from one collateral vessel to another. This sudden impairment of an already precarious circulation surely had a role in the appearance of gangrene, the extension of gangrene, or the failure of an amputated stump to heal. Anticoagulant therapy may have its main value in preventing or retarding the development or the propagation of this type of lesion in segments of a complicated anastomotic circulation.

Arterial calcification in the lower extremity has been noted frequently in young men free of any symptoms or signs of arterial insufficiency.[17, 18] It is found more often in the male than the female,[19] and is common in the diabetic.[20] Arterial calcification is said to be of some diagnostic value in distinguishing between arteriosclerosis and thromboangiitis obliterans in which it is absent or minimal.[19, 21] Possibly it is only an indication of early

arteriosclerosis. Intimal and medial calcification can perhaps be distinguished on the roentgenogram.[6, 19, 22] Some of our cases with relatively little arterial obstruction showed only medial calcification. In the majority, however, both intimal and medial calcification were present together in the same zone and, when extreme, even microscopic study could not always distinguish between them.

Others previously have reported a lack of correlation between arterial calcification and occlusion,[19, 21] and even an inverse relationship between the two.[6] It has been claimed[23] that calcified vessels when associated with hypertension show little tendency to thrombosis. Our own data clearly demonstrate this lack of correlation between calcification and occlusion in patients in whom the clinical picture of arteriosclerosis and gangrene was sufficiently severe to necessitate amputation.

Vagaries in the distribution of atherosclerosis throughout the arterial system were exemplified by the findings in the arteries of the lower leg. Any theory of the pathogenesis of atherosclerosis must take cognizance of the fact that the posterior tibial artery is usually the most extensively involved and the first in the lower leg to become occluded, that there are more occlusions in the popliteal branches than in the tibial artery branches and that, on occasion, two of the arteries in the lower leg may become completely obstructed and the third remain free even of an atheromatous plaque.

In a few extremities extensive gangrene occurred in the presence of relatively little occlusive disease and a demonstrable collateral circulation. The development of gangrene in such instances may, in part, be determined by superimposed factors such as shock, trauma, infection, and nutritional states which increase the discrepancy between supply and demand for blood beyond the limits which can be tolerated by tissues with a compromised circulation. A study of such clinical factors will be subsequently reported.

Summary

1. A new technic is described for the study of the arterial circulation of amputated extremities. The method is based on the use of a radiopaque injection mass containing lead and gelatin in appropriate proportions, and on a procedure for unrolling the extremity so that the major arteries lay in one plane. The properties of the mass and its value for studies of various organs are indicated.

2. The extent and location of arterial occlusion, narrowing, calcification and interarterial anastomosis were studied in 66 legs amputated because of arteriosclerotic gangrene.

3. One or more occlusions were found in each extremity examined; in 91 per cent of the legs two or more of the four major arteries were occluded usually at more than one point with an average of 11 sites of occlusion per leg. More than one-fourth of the lengths of these arteries was occluded by the time amputation was necessary.

4. In these arteriosclerotic limbs, the three lower leg arteries were the principal bottleneck in the flow of blood from the aorta to the toes.

5. The posterior tibial artery was invariably the first artery to be occluded and occlusions in this vessel were more extensive than in the other lower leg arteries.

6. Fresh completely occluding thrombi were present in about half of these extremities and in 25 per cent these fresh occlusions were multiple.

7. The roentgenologic demonstration of arterial calcification bore no relation to the presence or location of arterial occlusion. Examples were presented of markedly calcified arteries with little or no obstruction of the lumen as well as of arteries free of grossly visible calcification in which complete obstruction was found.

8. An extensive interarterial collateral circulation was clearly demonstrated. This rich anastomotic circulation permitted the occlusive disease to become extensive before gangrene supervened.

9. The clinical implications of these observations are discussed.

Sumario Español

Una nueva técnica se describe para el estudio de la circulación arterial de extremidades amputadas. El método se basa en el uso de inyección de substancia radiopaca conteniendo

plomo y gelatina y de un procedimiento de exponer la extremidad de manera que las arterias principales estén en un solo plano. Datos se presentan concernientes a la extensión y localización de la oclusión, estrechez, calcificación y anastomosis intrarteriales en 66 piernas amputadas debido a gangrena arteriosclerótica.

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A Study of Unipolar Left Back Leads and Their Application to Posterior Myocardial Infarction

By STEPHEN R. ELEK, M.D., LAWRENCE M. HERMAN, M.D., AND GEORGE C. GRIFFITH, M.D.

The electrocardiographic diagnosis of myocardial infarction of the posterior wall is often missed because it is largely dependent on lead aV_F and because this electrode position often does not subtend the diseased myocardium. To remedy this defect, a new method is described—unipolar left back leads. The validity of this method in registering potential from the posterior left ventricular wall is discussed as well as its importance in the diagnosis of myocardial infarction of the posterior wall. Left back leads can illuminate the significance of questionable Q waves.

THE VALUE of unipolar electrocardiographic leads taken from the anterior chest wall is well established. Posterior chest leads, however, are not usually employed because adequate systematic knowledge about them is not available. The greater distance separating the posterior chest from the heart might lead to the a priori assumption that back leads would not have sufficient "semidirect" relationship to the myocardial surface. This, in fact, was the conclusion of a recent study of back leads.[1] This view has lead to the use of esophageal leads as a semidirect approach to the posterior surface of the heart.[2-6] Aside from the obvious technical difficulties in using these leads, there is the further drawback that only a narrow portion of the heart is explored.

Wolferth and associates[6, 7] have studied the distribution of ventricular potential in leads taken from many regions of the body surface and showed that distance merely reduced the amplitude while the pattern remained faithfully reproduced. In their fundamental studies correlating electrocardiographic with postmortem findings in myocardial infarction, Myers and co-workers[8, 9] found that posterior myocardial infarction was most frequently missed and that the horizontal position of the heart contributed heavily to this failure. In 35 cases of necropsy-proven posterior infarction in hearts situated in the horizontal or semihorizontal position, 22 (63 per cent) showed a normal rS complex in lead aV_F. In 75 cases of proven posterior infarction with the heart in intermediate to vertical position, the electrocardiogram was negative in 16 (21 per cent). The failures were found almost entirely in patients whose lesions did not involve more than one third of the posterior left ventricular surface. In a necropsy study, Levine and Phillips[10] also noted that in 29 cases of old and recent posterior myocardial infarction 13 (45 per cent) were not diagnosed by the electrocardiographic studies.

Continental workers have attempted to increase the accuracy of diagnosis by using unconventional bipolar lead positions. Nehb[11] employed precordial position 7 and the second intercostal space just to the right of the sternum, while Slapak and Partilla[12, 13] used several points in the second intercostal space between the left sternal border and the anterior axillary line together with precordial position 7. Increased diagnostic accuracy was reported by these authors, but it is not clear what variations are found with these special leads in normal individuals. Sears and Myers[14] analyzed a limited number of left back leads and concluded that they were helpful in determining the presence and extent of posterior infarcts but failed in a few cases in which esophageal leads were positive.

The present study was undertaken to in-

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crease the accuracy of diagnosis of posterior wall infarction by the use of unipolar left back leads. The left back leads were studied in normal subjects, in patients with left and right ventricular hypertrophy, and in known and suspected cases of old and recent posterior myocardial infarction.

Method and Subjects

Unipolar V leads were taken along three vertical lines marked on the subject's left back. The spinous (Sp) line is drawn 2 cm. to the left of the thoracolumbar vertebral spines. The scapular (Sc) line represents the posterior projection of the anterior midclavicular line. The posterior axillary (PA) line is self explanatory. Points were marked along these lines for the placement of the electrode at the intersection of horizontal lines which passed through the spines of thoracic vertebrae 2, 4, 6, 8, 10 and 12, and lumbar vertebra 2. On the posterior axillary line recordings were made only at the level of the sixth and tenth thoracic and second lumbar spines. Each lead was labeled by the letters designating the vertical line and by the number designating the spinous level at which it was recorded. The level of the second lumbar spine was labeled L-2. Thus, Sc_8 represented the lead taken at the level of the eighth thoracic spine on the scapular line. Some idea of the anatomic relationships of the back leads may be gained from figure 1.

An early group of back tracings were taken with the subjects in the sitting position. Later it was found that somatic tremor was less troublesome when the subject was prone and the majority of tracings were taken in this position. Some acutely ill patients found it difficult to assume the prone position, and it was necessary to take the back leads while these patients were lying on their right side. In addition to the back leads, the usual 12 leads were recorded and the augmented limb leads were repeated with the subject in the position in which his back leads were taken.

The tracings were made with either a Sanborn Viso-Cardiette or a Beck-Lee Cardiall. In some cases the standardization was increased to one and one-half normal for the back leads to facilitate interpretation of weak potentials.

A total of 112 patients, divided as follows, was studied: 52 normal individuals, 18 patients with left ventricular hypertrophy, 6 patients with right ventricular hypertrophy, and 36 patients with posterior wall infarction. The normal subjects were either healthy medical students or patients without clinical or electrocardiographic evidence of heart disease. In the 52 normal subjects the electrical position was classified by the criteria of Wilson[15] as vertical (8 cases), semivertical (11 cases), intermediate (12 cases), semihorizontal (4 cases), and horizontal (17 cases). Because of the rarity of the horizontal electrical position in healthy young persons the group of normal subjects with horizontal hearts does not include any of the medical students but consists of an older age group, 40 to 65 years, with normal clinical, fluoroscopic and electrocardiographic findings.

Eighteen patients with clinical, fluoroscopic, and electrocardiographic evidence of left ventricular hypertrophy due to hypertensive heart disease without evidence of myocardial infarction were studied. The group with right ventricular hypertrophy consisted of six patients. Two had rheumatic heart disease with mitral stenosis, three were diagnosed as having cor pulmonale and one, in whom the diagnosis had been established by cardiac catheterization, had congenital heart disease with transposed pulmonary veins.

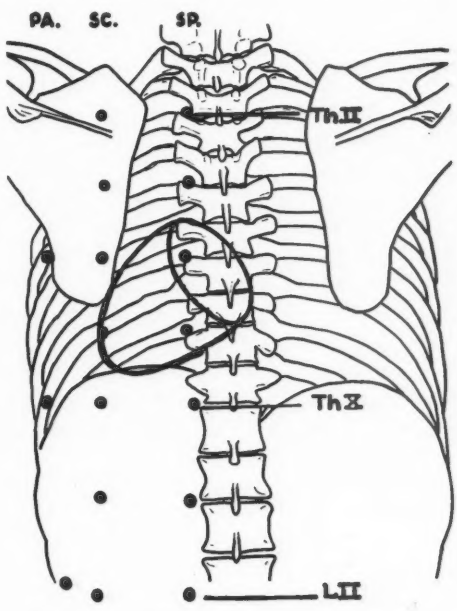

Fig. 1. Diagram showing position of the left back leads and their relation to the ventricles. See text.

There were 36 cases of posterior myocardial infarction: 21 were acute cases undergoing the typical clinical and laboratory course and electrocardiographic evolution during hospitalization, and 15 were cases with definite histories consistent with previous myocardial infarction. Electrical position can be only approximately determined in the presence of posterior infarction since lead aV_F is usually so altered that it cannot be used as a reliable guide[9]. By depending on aV_L these cases can be classified as horizontal to intermediate (qR or R

in aV_L), semihorizontal to semivertical (RS in aV_L), or semivertical to vertical (rs or QS in aV_L). When the terminal portion of the QRS in aV_F is upright, the height of this R wave aids in subclassification within the area defined by aV_L. None of our cases showed predominantly negative deflections in aV_L. The cases were classified into two groups: horizontal to semihorizontal position, 22 cases; and intermediate position, 14 cases.

Classification of QRS Patterns

Using Wilson's concepts[15] the initial ventricular complex may be separated into four patterns each representing the pattern obtained from a region of the heart: (1) the cavity pattern or QS wave, (2) the transition zone pattern, a QR wave, (3) the left epicardial pattern, a qR or R, and (4) the right epicardial pattern, rS or RS.

The cavity pattern is clearly distinguished from the transition pattern since the first appearance of an R wave as the electrode is placed more caudad marks the beginning of the transition pattern. Distinguishing the boundary between transition complex and epicardial complex raises a more difficult problem since both consist of a Q wave followed by an R wave. The transition zone pattern is recorded when the electrode is in such a position that it is affected by the current from both the endocardial and epicardial surfaces. It is apparent that as the electrode is shifted to a more caudad position relatively less of the endocardial and more of the epicardial potential will be recorded; hence, the Q wave becomes smaller. Therefore, the cavity Q wave must be distinguished from the small septal Q wave. This same problem is present in evaluating esophageal and aV leads. The form of the P and T waves has been used as a clue in determining when the electrode no longer faces any portion of the cavity. There are possible errors in the use of such clues, as will be discussed later.

Myers and co-workers,[9, 16] in evaluating the diagnostic significance of the Q wave in standard lead III and in aV_F, chose the following limits for a septal Q wave in aV_F: Q should not exceed 25 per cent of the voltage of R and should be less than 0.03 second in duration from onset to nadir providing the total voltage of the QR wave is 0.5 mm. or greater. These criteria seem adaptable for separating the transition Q from the septal Q in back leads. As a rule in normal subjects there was either no change in the ratio of Q to R, or only a slight and gradual reduction in the relative size of the small Q below the highest level (most cephalad) at which it may be classified as septal. On the other hand, above this level a majority of the records showed a much deeper and wider Q. Myers[9] had also noted that the duration and size of the septal Q wave is greatest near the base. This is the ground for the belief that the basal portion of the ventricular wall is activated last.

Results

A. Normal Subjects

The highest (most cephalad) levels in the left back leads in which the QRS complex reflected the epicardial potential was determined for the various heart positions. All the tracings taken on the posterior axillary line presented epicardial complexes. The tracings from the Sc and Sp lines showed variation in the level of transition from cavity QRS to epicardial QRS complex (table 1).

In the eight subjects with vertical position this transition was found between spinous level 6 and 10. Most of the cases showed the transition at Sc_8 and Sp_{10}. Figure 2 illustrates the vertical position. In the 16 subjects with horizontal hearts 14 presented epicardial complexes at Sc_2; the other two did so at Sc_4. The Sp line was slightly more variable but in 10 subjects the transition occurred at Sp_2 and Sp_4. In one example cavity Q waves were seen as low as Sp_{12}. In the Sp line of four subjects in the group with horizontal hearts the Q wave became relatively deeper compared with the R wave at levels below the epicardial transition. These were the only instances among normal subjects in which the Q wave became relatively larger as the electrode was moved caudad along a vertical line.

Twenty-seven subjects were included in the groups with semivertical, intermediate, and semihorizontal positions. In 20 subjects the transition was between Sc_8 and Sc_{10} while in 16 subjects the transition was between Sp_6 and Sp_{10}. There was some tendency for the transi

tion point to become higher on the scapular line and lower on the spinous line as the position became more horizontal. Some of the group with semivertical hearts showed low transition levels. It might be anticipated that if more examples of vertical hearts were studied, lower transition levels would be found in this group also.

The most consistent findings in the normal subjects were: (1) the presence of epicardial complexes in all the posterior axillary leads; (2) epicardial complexes at and below Sp_4 and Sc_4 in subjects with hearts in the horizontal position; and (3) the tendency for the Q wave to become smaller at more caudal levels along either line.

To test the usefulness of the P wave as a guide to the evaluation of the Q wave, the level of transition to an infra-atrial P was compared with the level at which the Q assumed the characteristics of a septal Q defined above (table 2).* Only normal subjects showing clearly defined P-wave transition levels were tabulated. The P wave was considered to be infra-atrial when it was entirely upright without an intrinsic deflection and with approximately equal ascending and descending limbs. It is apparent from table 2* that while commonly the P and Q waves changed at the same level there were many exceptions. Therefore, the P wave is not a reliable guide for determining the transition from cavity to septal Q.

Table 3* compares the level at which the Q wave meets the criteria of septal origin with the level at which the T wave becomes upright and at least one-tenth the height of R or at least 0.1 mv. in amplitude. There was only a small tendency for the T-wave change to occur at a higher level than the Q-wave change. In no instance did the T wave become upright more than two vertebral spine interspaces higher than the Q wave became septal. There were many examples of persistence of an inverted T after the Q wave had become septal. This was especially true with hearts in the horizontal position. The T wave, like the P wave, is not a reliable guide for determining the transition from cavity to septal Q.

Lead aV_F is known to record the potentials from the diaphragmatic surface of the heart and loosely this is considered to represent the posterior surface of the left ventricle. The degree to which it actually does record this ventricular wall depends on the position of the heart. It would be useful to know, in terms of practical electrode positions on the body surface, how large a portion of the posterior ventricle remains unrecorded by aV_F. In examining the back leads it was noted that the PQRST pattern in aV_F is mirrored in tracings recorded from the lower left back in essential details

TABLE 1.—*Highest Level Recording Septal Q Wave in Normal Subjects*

Vertebral Spine Level	Vertical			Semivertical			Intermediate			Semihorizontal			Horizontal		
	PA‡	Sc‡	Sp‡	PA	Sc	Sp	PA	Sc	Sp	PA	Sc	Sp	PA	Sc	Sp
2					1			3	1		2			14	8
4						1		1	1					2	3
6	2	2	1	2	3	1	1	1	2				3		
8		5	1		3	2		4	3		2				1
10		1	6		2	4		3	2		1	2			1
12					1	1									1
L_2															
0*					1	2			2			2			1
0†									1			1			1

* No septal Q wave seen—cases in which the lowest level recorded was 10

† No septal Q wave seen—cases in which the lowest level recorded was 12

‡ PA stands for posterior axillary line, Sc for scapular line and Sp for spinous line. (See text for further description.)

* Tables 2, 3, 4, 5, 6, 7 and 8 are omitted at the request of the Editor. They will be furnished on request.

except for absolute voltage. The distance between the highest back lead recording an epicardial complex and the highest reflecting the pattern of aV_F represents approximately the surface projections of the area of the posterior epicardial surface that is unrecorded by aV_F. Thus, in the Sc line of the patient with a horizontal heart, shown in figure 3, the area between Sc_2 and Sc_{10} records left ventricular

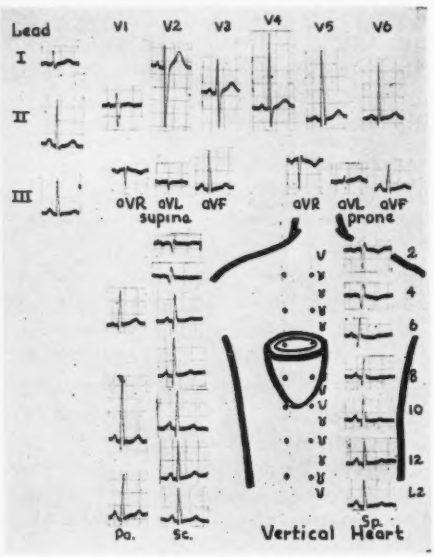

FIG. 2. The classic and left back leads in a typical normal subject with vertical heart position, showing relation of back leads to epicardium and cavity of heart. See text.

complexes which are not seen in aV_F. This can be tabulated as eight intercostal spaces of unrecorded posterior ventricular wall. Table 4* shows the distribution of this nonregistered area in spinous intercostal spaces in the various cardiac positions. In every electrical position most of the subjects presented some posterior epicardial surface hidden from lead aV_F. The unrecorded area tends to become greater in the horizontal position and less in the vertical position. Thus, among 16 subjects with hearts in the horizontal position, 14 presented hidden epicardial complexes over an area of 10 to 12 spinous intercostal spaces. There was only one subject in the group with vertical and semivertical hearts who had more than four hidden intercostal spaces. Subjects with hearts in intermediate and semihorizontal groups showed results between these extremes.

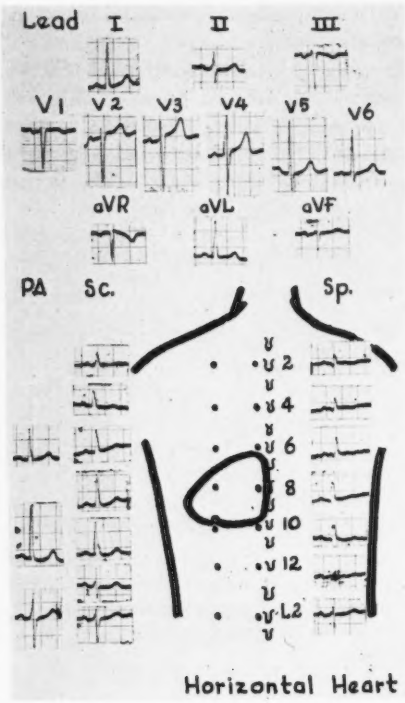

FIG. 3. The classic and left back leads in a typical normal subject with horizontal heart position showing relation of back leads to epicardium and cavity of heart. See text.

B. Subjects with Cardiac Pathology

1. Left Ventricular Hypertrophy. In most cases of left ventricular hypertrophy, the heart is in horizontal position with right ventricular QRS complexes in lead aV_F. Of the 18 cases of left ventricular hypertrophy, the hearts of 11 were horizontal or semihorizontal. Figure 4 illustrates the fidelity of recording of left ventricular complexes. Thus Sc_6 to Sc_{12} resemble V_5 or V_6 and Sp_{L2} resembles aV_F except for difference in voltage. Table 5* shows the distribution of the highest epicardial or septal Q wave using the criteria discussed above. In six cases in which PA

* See footnote p. 659.

leads were taken, epicardial complexes were seen at the highest level recorded (PA_6). In the Sc line, 13 of the 18 patients showed epicardial complexes in all leads from Sc_2 to Sc_{L2}. Four subjects showed transition to septal Q at Sc_4. One patient with vertical heart showed transition in Sc_{10}. The spinous line showed greater variability in the transition level.

Table 6* lists the unrecorded areas of the posterior ventricular wall measured in spinous intercostal spaces in the 11 cases of left ventricular hypertrophy in horizontal or semihorizontal heart position. This was determined in the manner described for normal hearts. In 10 of the 11 cases an area embracing eight or more intercostal spaces on the Sc line was hidden from aV_F. Again the Sp line was more variable. This left ventricular hypertrophy group, therefore, corresponds to the normal group with horizontal position in the large area of unrecorded left ventricle.

2. Right Ventricular Hypertrophy. In the three subjects with cor pulmonale who were in the horizontal or semihorizontal cardiac position, tracings made in the Sc line recorded right ventricular complexes from Sc_2 or Sc_4 down to Sc_{10} (leads were not taken at lower levels). The Sp line was variable; tracings made on this line showed right ventricular, left ventricular and cavity complexes. One case of mitral stenosis and insufficiency in the electrically vertical position, which also met the criteria of Sokolow and Lyon[17] for right ventricular hypertrophy, showed cavity complexes in all leads except Sc_{10}; the latter recorded a left ventricular complex. In the patient with transposed pulmonary veins, also in vertical position, left ventricular complexes were seen from Sc_6 to Sc_{L2} and from Sp_{12} to Sp_{L2}. The other leads recorded cavity complexes. The Sc line recorded right ventricular complexes at high levels. This is analogous to the recording of left ventricular complexes in the Sc line in horizontal normal hearts and horizontal left ventricular hypertrophy hearts.

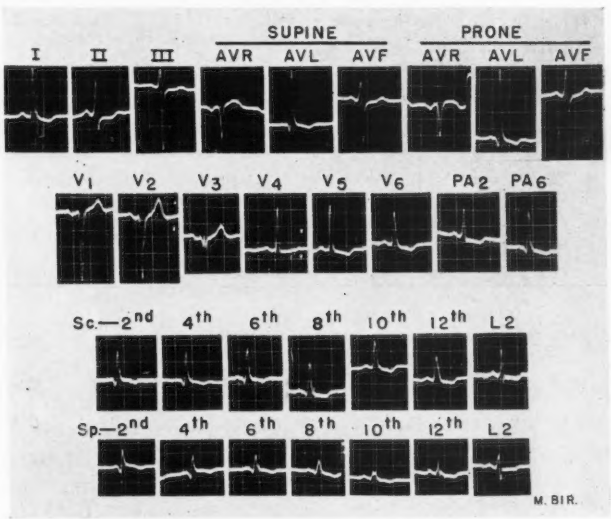

FIG. 4. Classic and back leads in a patient with left ventricular hypertrophy. Note that Sc_6 to Sc_{12} resemble V_5 and V_6 and Sp_{L2} resembles aV_F. See text.

3. Posterior Myocardial Infarction. In the 36 patients with posterior infarction who had definite electrocardiographic evidence of the infarct, normal left ventricular QRS complexes were seen at some level along either the Sp or Sc line on the back and a deep abnormal Q at a lower level along the same line. In all these cases a progressively deeper Q wave was noted as the electrode is moved from above downward

* See footnote p. 659.

over the area of the infarct. This is true for both the Sp or Sc lines although in some cases it was seen in the Sp line and not in Sc or vice versa. The deepening and often widening of the Q wave on descent of the electrode position could be demonstrated along the Sc line in all but four patients in whom tracings had not been made below Sc_{10}; when tracings were taken to the level of Sc_{12} or Sc_{L2}, the transition to abnormal was always demonstrable. The Sp line in four other cases failed to show a transition to a normal epicardial complex.

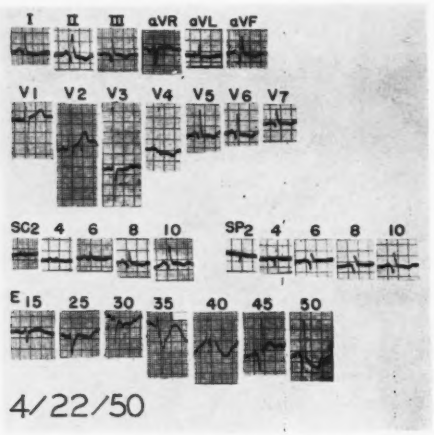

FIG. 5. Classic leads, back leads, and esophageal leads in a patient with posterior myocardial infarct. In E_{15} to E_{50} the numeral signifies centimeters from the teeth. See text.

In two of these subjects, the presence of infarction was apparent from the progressive deepening of the Q wave at lower levels. In the other two cases, the Sp line was not diagnostic since the QR ratio remained relatively constant at all levels.

The highest levels in the back leads at which the presence of infarct could be established were charted (table 7).* At least one higher lead showed a Q wave which could be accepted as septal in origin. The area between Sc_8 and Sc_{12} and between Sp_6 and Sp_{10} included the vast majority of the upper limits of demonstrable infarction. Since all these subjects showed an abnormal Q in aV_F, they also recorded an abnormal Q in all back leads below the highest level indicative of infarction. In a substantial number of our cases, Q waves caused by infarcts were found on a large area of the back and may be presumed to indicate a large area of infarction of the posterior ventricular wall. The size of the infarct, of course, could not be ascertained from aV_F.

The area of infarction not reflected in aV_F was evaluated in a manner analogous to the estimation of unrecorded ventricular surface in the subjects with normal or hypertrophied hearts. The results are shown in table 8.* In 19 subjects with hearts in a horizontal and semihorizontal position in whom infarction could be diagnosed by the Sc leads, 18 showed extension along the Sc line beyond the area reflected in aV_F. In six, the unrecorded portion of the infarct projected for two spinous intercostal spaces; in seven, for four intercostal spaces; and in six, for six intercostal spaces. The Sp line showed more variability since there were four instances of 8 to 12 unrecorded intercostal spaces of infarction. However, since some of the normal subjects with horizontal hearts showed abnormal Q waves in the Sp line, the evidence points to the Sp line as being less dependable than the Sc line. In patients with hearts in the intermediate position, more of the infarcted area was reflected in aV_F. In both Sp and Sc lines, 4 out of 15 cases had more than two unregistered intercostal spaces exhibiting infarction.

C. Correlation with Esophageal Leads

Five patients with definite evidence of posterior infarction were studied with both back leads and esophageal leads at 2.5 to 5.0 cm. intervals. The latter leads also demonstrated the infarct. In patient L.S. (fig. 5) the esophageal leads give the impression of a high posterior infarct beginning just inferior to the atrium, while the back leads give the impression of normal muscle just inferior to the atrium with the infarcted area at a lower level. This is best seen in Sc_6. While it is possible that esophageal leads taken at closer intervals might have shown normal epicardium

* See footnote p. 659.

between atrium and infarcted area, it is noteworthy that this was not found in the five cases studied. On the other hand, the back leads in all five cases did show a transition from normal to infarcted epicardium. Because of disagreement in interpretation of the esophageal leads[4] in this region, we are unable to correlate the esophageal with the back lead findings with regard to the more exact localization of the infarcted area.

Two patients in whom the back leads did not demonstrate infarction were studied with esophageal leads. These patients had typical clinical histories of acute myocardial infarction two weeks prior to our study. Very small Q waves in leads II and III were the suggestive electrocardiographic findings. The esophageal leads resembled the Sp leads and showed ST-T changes at low levels but pathologic Q waves were not obtained. In these two cases, the esophageal leads gave no more information than the back leads.

One patient was studied in whom the clinical picture was suggestive of infarction, but the conventional 12-lead electrocardiogram was not diagnostic at first. In this patient, the back leads showed serial evidence of infarction as illustrated in the following summary:

Patient M. L., 65 year old male, is illustrated in figure 6. He was first seen on June 9, 1951, about 90 minutes after the onset of severe substernal pain radiating to the left shoulder precipitated by attempting to chop down a tree.

The classic leads showed S–T elevation in aV_F, II, and V_6, suggesting lateral and possibly posterior ischemia. The horizontal heart position prevented the recording of the posterior epicardial surface in aV_F. In this position it is anticipated that the Sc leads will reflect epicardial surface at or below Sc_2. The tracings show that the Q in Sc_4 is relatively larger than Q in Sc_2 and that from Sc_6 through Sc_{10} the unmistakable evidence of very acute infarction with tendency to monophasic ventricular complexes is present. Sc_{12} and L_2 illustrate the transition to right ventricular complexes normally seen in horizontal hearts.

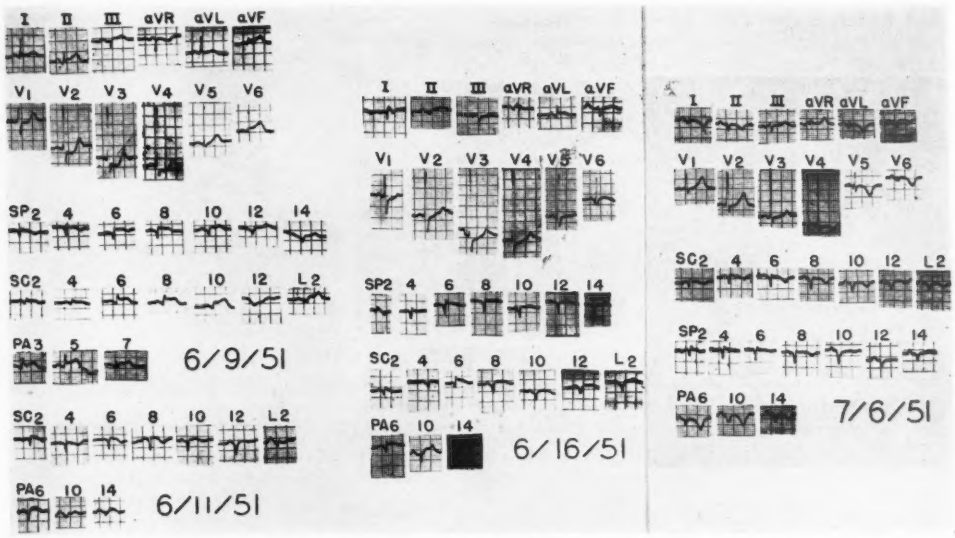

FIG. 6. Serial electrocardiograms in patient M. L. showing evolution of a recent posterior wall infarct diagnosed earlier in the back leads than in the classic leads. Sp_{14} is the same as Sp_{L2}. See text.

The clinical course and laboratory studies of this patient showed the blood pressure drop, the febrile reaction, the leukocytosis, and increased sedimentation rate characteristic of acute infarction. On June 16, 1951, there were minor changes in the classic leads consisting chiefly of a small Q wave, beginning inversion of T wave in lead aV_L and lead I, and less S–T elevation. The back leads in the Sc line showed the usual serial changes seen in infarction. The small R wave in Sc_{L2} had disappeared (extension through

posterior septum?). Tracings made in the PA line definitely showed the lateral extension which had been hinted by aV_L. On July 6, 1951, the first unequivocal evidence of infarction in classic leads was seen and the area of ischemia had extended laterally (V_5 and V_6). Back leads showed the expected serial changes with progressive inversion of T waves in the infarcted area.

From the evidence in the back leads we could postulate a large posterior infarct at the first examination while the classic leads were only suspicious. Extension to the septum and laterally was demonstrable in subsequent tracings. The Sp leads were not informative of myocardial infarction and evidently represent cavity or transitional complexes. Therefore, the diagnosis was dependent on changes in the Sc line. The important diagnostic lesson is that the back leads showed the posterior myocardial infarction earlier than the classic leads because the back leads subtend the infarcted region.

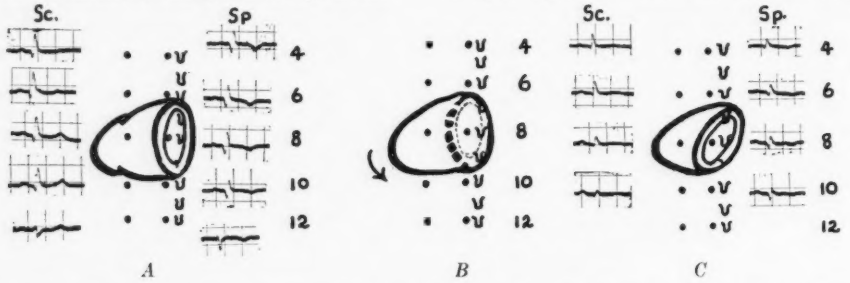

FIG. 7. Schematic explanation for progressively deeper Q waves in the Sp lead in normal hearts in the horizontal position. See text.

A. The base is almost parallel to the Sp line. Cavity or transitional complexes are recorded in all Sp leads, except Sp_{12}. *B*. With posterior rotation of the apex, epicardial complexes are recorded in Sp leads. (See also fig. 3.) *C*. The apex is rotated cephalad so that the superior portion of the base lies more medially than the inferior portion. More of the cavity is recorded in the lower Sp leads than in the upper Sp leads.

DISCUSSION

In this investigation of the left back leads, a major problem was the differentiation of the cavity Q waves from Q waves caused by infarction. This necessitated a study of the back leads in normal and abnormal hearts in various electrical positions. Figures 2 and 3 illustrate rather typical findings in left back leads in vertical and horizontal hearts. In the vertical heart (fig. 2), both Sp and Sc leads show a recognizable progression from cavity to transitional to left epicardial complexes. Leads Sp_2 and Sc_2 subtend the cavity in the same manner as lead aV_R, and accordingly, these complexes closely resemble each other. Leads Sc_8 to Sc_{L2} and Sp_{12} to Sp_{L2} subtend the epicardial surface of the left ventricle in the same manner as leads V_5, V_6 and aV_F, and again these complexes closely resemble each other (except for differences in voltage). Transitional complexes obtained partly from the cavity and partly from the epicardium are recorded in Sc_4 to Sc_6 and Sp_4 to Sp_8. The PA leads reflect only epicardium since they do not face the cavity.

In the normal heart in the horizontal position (fig. 3) only Sp_2 "looks" partially into the cavity, whereas PA, Sc and the remaining Sp leads reflect either right or left epicardial complexes, or transitional complexes along the septum as noted in Sp_{12} and Sc_{12}. This transition from left to right ventricular complexes resembles that seen in the precordial leads. Figure 3 also demonstrates for the first time that the rS complex seen in aV_F in horizontal hearts is also transmitted to the left back leads so that the right ventricle not only rests on the diaphragm but also points posteriorly.

With the exception of the horizontal heart position, the transition from cavity to epicardial complexes occurs at varying levels in the other electrical positions. Hence, the significance of the Q wave must be evaluated by comparing the various back leads in a given individual. The registration of a deep, wide Q wave at any given back position may not be indicative of infarction. However, once the transition to a septal Q wave is recorded the

finding of a cavity-like Q wave at a lower level in the same line is abnormal. This type of evaluation is similar to the interpretation of a small or absent R wave in lead V_3. With sufficient clockwise rotation, V_3 normally records a cavity complex and a small or absent R wave is expected. However, if the same patient had a definite R wave in lead V_2, the absent R in V_3 is abnormal.

There were four exceptions to this empiric finding, all in the Sp line in normal hearts in the horizontal position. In these patients the depicted in figure 7. In figure 7*a* the plane of the base of the heart is almost parallel to the Sp line so that cavity or transitional complexes are noted in both high and low Sp leads. As the apex rotates more posteriorly (fig. 7*b*) the plane of the base of the heart faces more anteriorly so that the Sp line does not "look into" the cavity and epicardial complexes are registered. This is also illustrated in figure 3. When the superior portion of the base lies more medially than the inferior portion (fig. 7*c*), upper Sp leads will show transitional complexes.

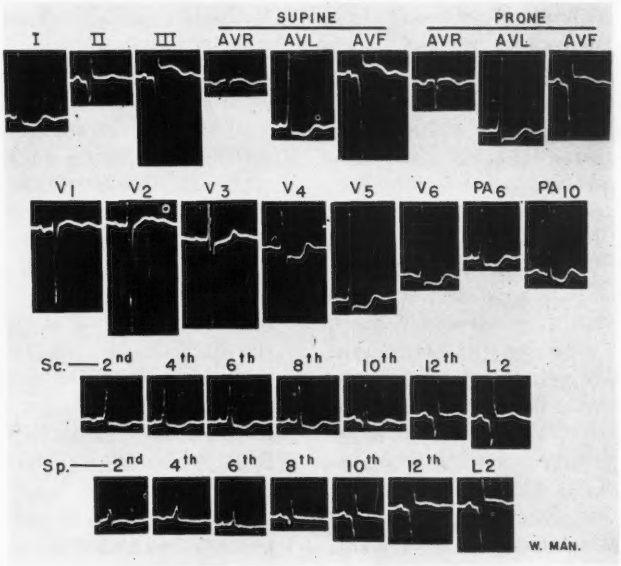

Fig. 8. Classic and back leads showing digitalis effect in a patient with posterior myocardial infarction. See text.

Q wave became progressively deeper from Sp_2 to Sp_{10}, although normal left ventricular complexes were present in the Sc leads. Also, the transition from right to left ventricle in the precordial leads occurred at V_5 and the initial R in aV_R was absent. These four exceptions may be explained by considering the relationship between the Sp line and the base of the heart. When the heart is horizontal, the Sp line tends to be in the same sagittal plane as the base. Accordingly, relatively minor mediastinal or apical shifts may determine whether cavity or epicardial complexes are recorded in the Sp line. Our suggested hypothesis is The four exceptions in the normal horizontal hearts may fit into the concept diagrammed in figure 7*c*.

In the 112 patients studied, the left back leads obtained in normal hearts and in those with the various cardiac lesions record with surprising fidelity (except for voltage) not only the QRS complexes but also the ST-T changes of left ventricular hypertrophy and/or strain (fig. 4), and in one patient digitalis effects (fig. 8). The back leads also register a considerable area of the posterior left ventricular surface not recorded in aV_F, especially in the semihorizontal and horizontal heart position.

It should also be noted that only minimal changes occur in the aV leads in the supine or prone posture so that this posture hardly influences the cardiac electrical position.

Margo and Foscarini[1] were unable to correlate posterior chest leads with anatomic or clinical conditions and felt that the exploring electrode is so far distant from the heart that cavity and epicardial potentials cannot be distinguished. These authors used leads on a plane with V_6 equivalent to our PA_{10}, Sc_{10}, and Sp_{10} plus Sc_{10} on the right back. Their leads, limited to a horizontal plane in the back, do not permit analysis of transition from cavity to epicardial complexes which is the basis of our study. Our study shows that multiple leads along a vertical line in the back are necessary for proper interpretation. Also, our evidence indicates that left back leads are semidirect leads and yield localized information about the posterior heart surface.

The criteria of Myers[9, 16] for infarction Q waves in lead aV_F is supported by his necropsy data. The finding in the back leads that the Q wave becomes progressively deeper (and occasionally wider) as the electrode is moved caudally on a vertical line, even though the largest Q wave may fall short of satisfying Myers' criteria, is highly suggestive of myocardial infarction, and particularly so in the Sc line. This has been seen in patients with clinical and electrocardiographic evidence of posterior myocardial infarction. However, postmortem correlation is necessary for confirmation.

From the results in our five cases of myocardial infarction studied by both esophageal leads and left back leads it would appear that the former tend to record deep Q waves over a relatively wider area than the latter. This may lead to the false diagnosis of high infarcts by esophageal leads and perhaps prevent the diagnosis of such infarcts by the back leads. The esophageal leads are limited to one vertical line and may leave much of the posterior surface unexplored. The back leads do not have this limitation. When a heart is in the horizontal position, the esophagus may be in a particularly disadvantageous relationship to the ventricle. The esophageal electrocardiogram will represent chiefly the uppermost base of the ventricles and the proximity of the A-V groove could lead to errors in interpretation. This is suggested by our finding that the Sp line is unreliable in horizontal heart position and this line roughly parallels the esophagus.

The criteria for the diagnosis of posterior infarction in the back leads may well be applied to studies with esophageal leads. The significance of a deep Q wave cannot be based solely on the form of the accompanying P wave. That this is true for the esophageal leads has been recently demonstrated by Sandberg and associates[5] and our results with back leads tend to be confirmatory. That rigid application of the P-wave criterion can lead to apparent over-diagnosis of high posterior infarction is illustrated in a recent report by Benchimol and co-workers.[18] Their cases 9 and 10 were presented as diagnostic of infarction although there was only a rather vague past history and no other objective confirmation. Their cases showed moderately deep, narrow T waves for 2.5 to 5 cm. below the level at which the P lost its intrinsic deflection. However, in each case the T waves became progressively smaller as the recording electrode moved from the cavity to the transitional to the epicardial zones. From our study of left back leads, we would consider these cases as showing a normal tendency for transition of the Q wave at a slightly lower level than the P wave rather than indicating infarction. Neither the P wave nor the T wave may be reliable guides for evaluating the meaning of a deep Q wave. Instead, the demonstration of deepening Q waves as lower left back leads are recorded would be more dependable guides.

Patients in whom posterior infarcts are most likely to be missed by routine electrocardiography are those whose hearts are in semihorizontal to horizontal positions.[9, 10] These include most cases of left ventricular hypertrophy. This explains the high incidence of posterior infarction not diagnosed in the usual electrocardiogram in Myers' series. Fortunately in these cases most, if not all, of the PA and Sc leads represent the epicardial

surface and a wide area is available for exploration. It is in such patients that left back leads are most likely to find application. The present results also suggest that in some cases with more vertical heart position a significant area of posterior infarction may be diagnosable only by back leads. In subjects in whom the presence of infarction is established by other leads, the back leads could be helpful in demonstrating the extent of infarction.

The introduction of new electrocardiographic leads raises the question whether the additional information gained warrants the added time involved. The left back leads are not indicated for routine use. They should serve to supplement the routine leads when an equivocal Q wave is found in aV_F or when a clinically suspected myocardial infarct is not demonstrated by routine methods. In these problems the back leads may substitute for esophageal leads and are easier to take. The entire series of 17 posterior leads is often not necessary in clinical problems. The Sc line is usually most productive of useful and reliable information. If Sc_{L2} is recorded first and successively higher leads are taken along this line one may gather this information with a minimal number of leads. A large Q wave at a low position and an epicardial complex at a higher position are the significant findings. Occasionally this may be seen after only three or four leads. When the entire Sc line is normal, then exploration of the PA and Sp lines in a similar manner is indicated.

Summary

1. Unipolar left back leads are semidirect leads; they recorded with fidelity the electrical events of the posterior surfaces of the left or right ventricles, and the cavity in the 112 patients studied.

2. In normal subjects with hearts in the horizontal position consistent recordings of epicardial complexes are found in tracings made in the PA and Sc lines. With the heart in other positions, transitions from endocardial to epicardial complexes are found along the Sc and Sp lines at variable but recognizable levels, while the tracings made in the PA line record only epicardial complexes.

3. In right and left ventricular hypertrophy changes similar to those seen in the conventional leads are recorded in the back leads.

4. In all 36 cases of posterior myocardial infarction established clinically and by conventional electrocardiographic leads, the back leads also showed the infarct. In addition, the back leads showed the transition from unaffected posterior ventricle to the area of infarction (that is from septal Q to infarct Q), and thereby allowed some estimation of the size of the infarct. In some patients clinically suspected of myocardial infarction, in whom the conventional leads did not clearly demonstrate the infarct, the left back leads offered specific evidence of infarction.

5. In every electrical heart position, most of the normal and abnormal patients presented some posterior epicardial surface hidden from lead aV_F. This electrocardiographically unrecorded area is least in the vertical position and most in the horizontal position.

6. An interesting finding in the back leads, noted for the first time, was a transition from left to right ventricular complexes in horizontal hearts in either normal subjects or patients with left ventricular hypertrophy. This may be comparable to a similar transition seen in the precordial leads.

7. A concept is advanced that progressive deepening of the Q wave as the lower left back leads are recorded may indicate myocardial infarction just as well as the accepted criteria for an abnormal Q wave in lead aV_F. Thus, the significance of questionable Q waves in lead aV_F, upon which the diagnosis of posterior myocardial infarction usually depends, can be better evaluated by means of the left back leads.

Sumario Español

El diagnóstico electrocardiográfico de infarto de la pared posterior del miocardio es a menudo pasado por alto debido a que depende grandemente en la derivación aV_F y debido a que la posición del electrodo muy a menudo no subtiende el miocardio averiado. Para remediar este defecto, un método nuevo se describe—derivaciones unipolares del lado izquierdo de la espalda. El valor de este método registrando

potenciales de la pared posterior del miocardio se discute asi como su importancia en el diagnóstico de infartos posteriores del miocardio. Derivaciones del lado izquierdo de la espalda pueden iluminar el significado de ondas Q de origen problemático.

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The Bronchoscopic Measurement of Left Auricular Pressure

By P. R. Allison, F.R.C.S., and R. J. Linden, M.B., Ch.B.

A specially adapted needle on the end of a Jackson's suction tube has been used to pierce the left auricle of the heart through the upper end of one of the main bronchi. Pressure measurements and wave forms have been recorded in patients suffering from lung disease with normal hearts, in those with mitral stenosis and mitral regurgitation. This preliminary communication describes the method and shows some typical results.

THE ONLY CHAMBER of the heart not so far accessible to direct pressure measurement has been the left auricle. The surgery of mitral stenosis has increased the need for information about the hemodynamics of the left auricle, and the present investigation was planned as a contribution to this end. Although much has been learned from the measurement of pulmonary capillary pressure, there has been no proof that this reflects all the changes that may occur in the left auricle. There has certainly been a need to investigate this, and the direct approach has therefore been undertaken.

The left auricle is so closely related to the esophagus behind, the bifurcation of the trachea above and the two bronchi on each side that these channels presented an obvious method of approach. Experience in the measurement of pressures in esophageal varices through the esophagoscope, and in the aspiration of congenital bronchial cysts through the bronchoscope had already been obtained, and it seemed an easy thing to apply this experience to direct puncture of the left auricle. Trials on the cadaver showed that it was equally easy to pass a needle into the auricle through the esophagoscope at a point about 30 cm. from the alveolar margin, or through the bronchoscope at the level of the carina or upper end of one of the main bronchi. The latter path seemed to be the cleaner one as swabs taken from this region when there is no obvious respiratory infection are always sterile. It was this approach, therefore, that was finally adopted for the living patient.

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Anatomy

The bifurcation of the pulmonary artery lies anterior to the lower end of the trachea and the carina. Immediately below the bifurcation of the pulmonary artery lies the left auricle and as this bulges backwards into the concavity of the thoracic spine it lies between the two main bronchi. The superior pulmonary veins lie in front of the bronchi, and the inferior veins pass behind the bronchi. The line of the anterior wall of the trachea, if prolonged downward, would pass through the pericardium behind the pulmonary artery into the left auricle.

Apparatus

The apparatus consists of a standard membrane manometer filled with fluid to which a "catheter-like" tube and a needle are attached. The needle is fused to a metal bronchus-aspirating tube 50 cm. long and with 2 mm. bore, which is attached to the manometer by a length of rigid polythene tubing of 3 mm. bore. The length of the tubing is kept at a minimum, but a convenient length for ease of insertion is found to be 40 cm. (fig. 1).

The system was found to have an undamped natural frequency of 50 cycles a second, and although it is realized that components of the fundamental pulse wave oscillating at more than 25 cycles a second will not be recorded faithfully, it is considered that this factor will produce negligible distortion of the fundamental pulse wave itself, when the system is critically damped. Damping has been achieved by using the puncturing needle as the damping needle, this having the advantage of preventing free damped vibrations in the fluid system. The minimum length for insertion into the left auricle is 4 cm. so that the needle must be at least 5 cm. in length.

Critical damping was found by the method of Warburg,[1] and in the present work a figure between

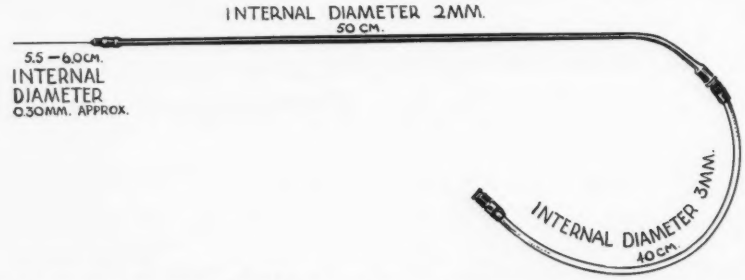


FIG. 1. Drawing of the needle welded to a bronchoscopic aspirating tube used for puncture of the left auricle of the heart.

FIG. 2. Drawing of the view down the bronchoscope showing the carina, and the needle piercing the anteromedial wall of the right main bronchus.

0.7 and 0.8 has been accepted. The needles which complied with these requirements were approximately of 0.3 mm. bore and 5.5 to 6.0 cm. in length, and were most easily made from British wire gage, number 24 needles. Trial and error, with various needles, was thought to be a better way of finding optimum damping, than calculation, which would in itself require experimental proof.

Great care should be used in filling the fluid system, for a small air bubble will cause overdamped tracings. To show up such an error it is useful to apply a square wave impact immediately after setting up the apparatus and before each set of recordings. Vibration of the system must be prevented, and to this end efforts are now being made to eliminate the polythene tubing and use the needle manometer system as a single rigid instrument.

TECHNIC

The patient is given 10.0 mg. morphia and 0.6 mg. atropine for premedication. The throat and larynx are painted with 2 per cent Amethocaine hydrochloride and a few drops of this are instilled into the trachea. The adult Negus bronchoscope is passed down to the carina and this too is sprayed with the local anesthetic. A swab has been taken from the medial wall of the right main bronchus for bacteriologic examination, and this, so far, has always been sterile. The needle on the cannula, connected to the manometer and filled with saline-heparin solution, is introduced into the bronchoscope, and, with the solution dripping, it is passed through the anteromedial wall of the right main bronchus at the carina (fig. 2). The needle passes about 4 cm. before entering the auricle but this depends a little on the size of the chamber.

RESULTS

The present communication is mainly to describe a simple technic for measuring left auricular pressures rather than to draw conclusions from the small number of results so far obtained. The following preliminary observations have been made: (1) Bronchoscopic measurement of left auricular pressure in control patients suffering from some disease other than mitral stenosis for which a thoracot-

omy was to be done (fig. 3 *A*); (2) comparison of the pressures and wave forms obtained by puncture through a bronchus in control subjects with those obtained by direct puncture of the left auricle at thoracotomy, using the same needle-manometer system (fig. 3 *B*); (3) repetition of the above observations in patients with mitral stenosis (fig. 4); (4) repetition as above in patients with mitral regurgitation (fig. 5); (5) simultaneous recording of left auricular pressure and pulmonary capillary pressure in patients suffering from mitral stenosis (figs. 6 and 7).

Samples of the tracings are presented. Although these electrocardiograms and phonocardiograms were recorded simultaneously with the left auricular pressures, they have been separated and remounted in order to save space. These are necessarily selected ones. Many more have been done during the experimental period. Their main value has been to show how distortion and interference can

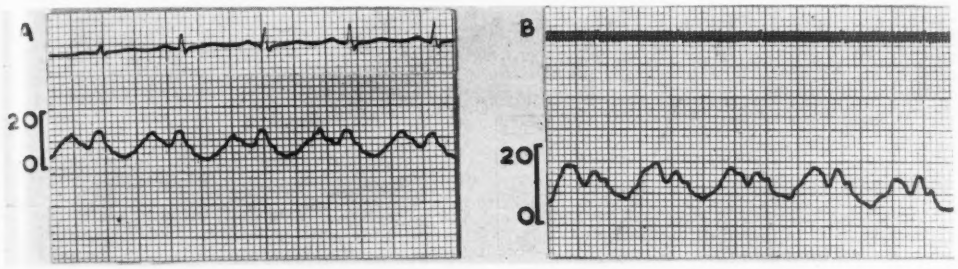


FIG. 3. Normal heart. Carcinoma of bronchus. Upper record, electrocardiogram. Lower record, left auricular pressure. Paper speed 25 mm. per second. Calibration in cm. H_2O. Same manometer system used in each recording.

(*A*) Obtained through the right bronchus. Arterial blood pressure 140/80. Zero leveled to manubrium sterni, patient supine. (*B*) Direct measurement through the open chest at operation. Arterial blood pressure 115/70. Zero leveled to mid left auricle, patient on left side.

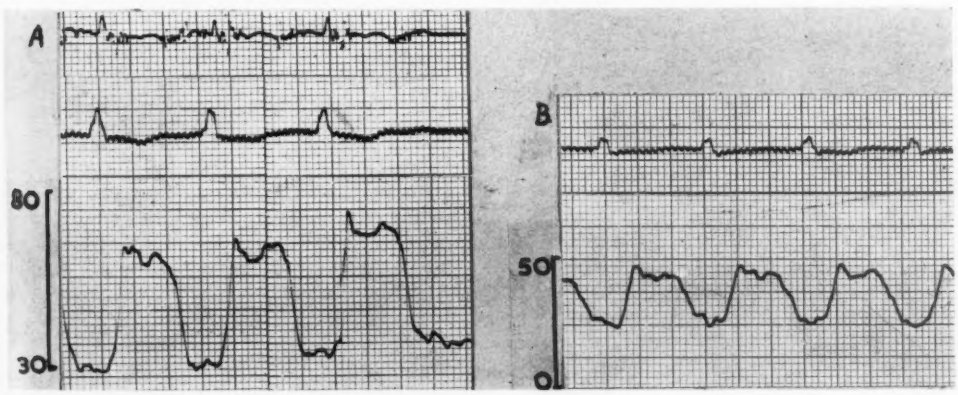


FIG. 4. Mitral stenosis. (*A*) From above down, records are phonocardiogram, electrocardiogram and left auricular pressure (obtained through right bronchus). Arterial blood pressure 120/80. Zero leveled to manubrium sterni. Paper speed 50 mm. per second. (*B*) Upper record, electrocardiogram. Lower record, left auricular pressure by direct puncture through open chest at operation. Arterial blood pressure 85/50. Zero leveled to mid left auricle, patient on right side. Both tracings show a little mechanical interference due to oscillation of the polythene tubing.

The same manometer system was used in each recording. Calibrations are in cm. H_2O.

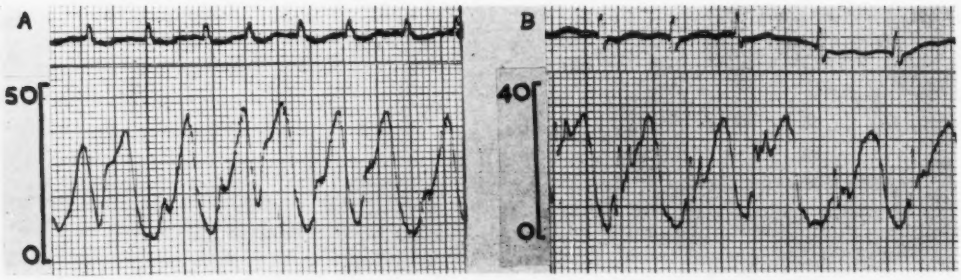
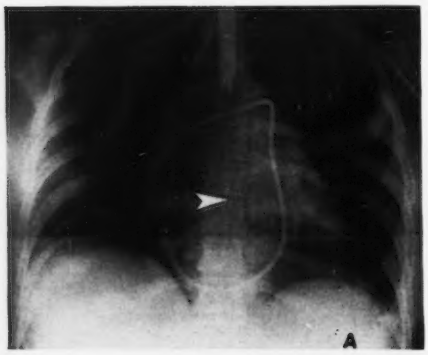


FIG. 5. Mitral regurgitation. Upper record, electrocardiogram, lower record, left auricular pressure. Paper speed 25 mm. per second. Calibration in cm. H_2O. Same manometer system used in each recording.

(*A*) Obtained through the right bronchus. Arterial blood pressure 135/90. Zero leveled to manubrium sterni, patient supine. (*B*) Direct measurement through the open chest at operation. Arterial blood pressure 105/80. Zero leveled to mid left auricle, patient on right side. This record shows mechanical interference due to oscillation of polythene tubing.



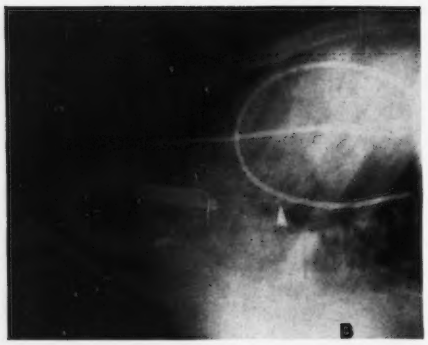


FIG. 6. *A* and *B*. Anteroposterior and lateral radiograms of the chest of a patient with mitral stenosis, showing the cardiac catheter jammed in the periphery of the pulmonary vessel, and the bronchoscopic needle in the left auricle of the heart. Tip of needle is indicated by arrow. Simultaneous records are shown in figure 7.

occur, and what factors are mainly responsible for these. Difficulties arise from doing such work in unscreened rooms in a big general hospital where diathermy sets and short wave therapy are in constant use. In recent work the obvious advantage of simultaneous electrophonograms as well as electrocardiograms has been appreciated. No harm has come to any of the patients examined. Where operation has been performed, no trace of the puncture has been seen, except in one patient with huge pulmonary arteries and a pulmonary pressure equal to her systemic pressure. In this patient the pulmonary artery was punctured by passing the needle too far forward, and at operation there was slight excess of pericardial fluid, which was blood stained.

The only opinions that seem tenable at this stage of the investigation are: first, that the pressure tracing in the left auricle in a normal individual consists of a smooth double wave; second, that any subsidiary waves are caused by extraneous interference; third, that the wave form in mitral stenosis is similar to that in the normal, but that absolute pressures may be raised, and that this is so whether the auricle is fibrillating or not; fourth, that in gross mitral regurgitation the second wave climbs above the first with only a slight depression between the two; and fifth, that although the wave form in the left auricle may in certain circumstances be similar to that in

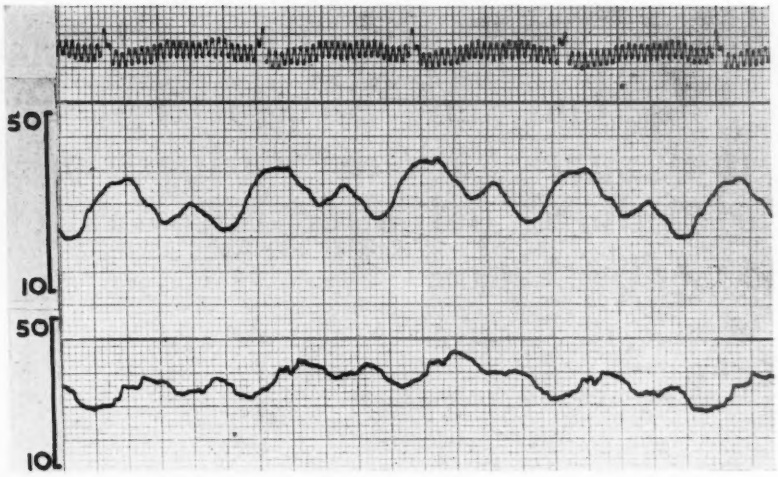


FIG. 7. Mitral stenosis. Simultaneous record of left auricular pressure and pulmonary "capillary" pressure. Records, from above down, are electrocardiogram, left auricular pressure and pulmonary "capillary" pressure. Left auricular pressure was recorded through the right bronchus, and the pulmonary "capillary" pressure through a number 8 catheter securely jammed in the periphery of the lung. Arterial blood pressure 130/80. Zeros on both manometers were leveled to manubrium sterni. Calibrations in cm. H_2O.

the pulmonary capillaries, this is by no means always so, and that the catheter jammed in the periphery of the lung is an unreliable way of estimating what goes on in the left auricle.

It will be noted that as yet no claim can be made that small degrees of regurgitation can be detected, and it has not been possible to estimate the mobility of the valve cusps from tracings obtained. It is hoped that extensive use of the method combined with careful appraisal of the heart at operation may, in the future, give useful information before operation.

SUMMARY

1. A method is described for direct measurement of the pressure in the left auricle by means of a needle introduced through the bronchoscope.

2. Some of the difficulties of establishing such a recording system are discussed.

3. Pressure wave tracings are presented from patients with normal hearts, mitral stenosis, and mitral regurgitation.

4. The pressure and wave form in the left auricle have been compared with those taken simultaneously from a catheter jammed in the periphery of a pulmonary vessel.

SUMARIO ESPAÑOL

Una aguja especialmente adaptada al terminal de un tubo de succión de Jackson se ha usado para penetrar la aurícula izquierda del corazón a través del terminal superior de uno de los bronquios mayores. Determinaciones de presiones y ondas se han registrado en pacientes padeciendo con enfermedad pulmonar con corazon normal y otros con estenosis mitral y regurgitación. Esta comunicación preliminar describe los métodos y muestra algunos resultados típicos.

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Cardiovascular Dynamics, Blood Volumes, Renal Functions and Electrolyte Excretions in the Same Patients during Congestive Heart Failure and after Recovery of Cardiac Compensation

By Ludwig W. Eichna, M.D., Saul J. Farber, M.D., Adolph R. Berger, M.D., David P Earle, M.D., Bertha Rader, M.D., Edmund Pellegrino, M.D., Roy E. Albert, M.D., J. Deaver Alexander, M.D., Harry Taube, M.D., and Sol Youngwirth, M.D.

Largely on the basis of acute observations in cardiac patients during congestive heart failure and in noncardiac control subjects, two assumptions have been made: (a) that congestive heart failure develops as cardiovascular and renal functions change from the type found in the control subjects to the type found in decompensated cardiac patients, and (b) that a return to, or toward, the normal occurs in these functions as cardiac compensation is regained. That these assumptions are not necessarily valid is indicated by the herein reported simultaneous measurements of cardiovascular dynamics, renal functions, blood volumes and electrolyte excretions in eight patients during cardiac decompensation and after recovery of compensation.

NUMEROUS recent studies have established the pattern of the changes in cardiovascular dynamics, renal functions, blood volumes and fluid and electrolyte excretions in congestive heart failure. This information has been derived almost wholly from comparisons of two separate groups of subjects; one, a group of patients with congestive heart failure, the other, either a group of subjects without heart disease or a group of compensated cardiac patients. Furthermore, the comparisons have usually been limited to determinations of one, or at most several, functions. Since the quantitative level of cardiovascular and renal function varies considerably from subject to subject, these studies do not establish the degree of change in a given function during recovery from congestive heart failure. Furthermore, they do not determine the relationships between the changes in the various functions as cardiac compensation is regained. Such information is best obtained by simultaneous measurement of the changes in many functions in the same subjects during congestive heart failure and after recovery therefrom. Of the several studies[1-3] of this type which have been attempted, only the observations of Briggs, Fowell, Hamilton, Remington, Wheeler and Winslow[1] are practically complete, the others are each incomplete in some respect.

In the present study simultaneous measurements were made of the cardiovascular dynamics, blood volumes, renal hemodynamics and water and electrolyte excretions of eight cardiac patients while they were in congestive heart failure and again after they had recovered cardiac compensation. A comparison of these data for the two states of cardiac competence should serve to indicate the degree of change in each function and the interrelationships between the changes in the various functions, as compensation from congestive heart failure is achieved.

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This study was assisted by Grants in Aid from the New York Heart Association, Inc., and the Life Insurance Medical Research Fund.

Drs. Rader, Alexander and Youngwirth are Fellows of the New York Heart Association, Inc.

Dr. Albert is a Post-Doctorate Fellow, United States Public Health Service.

Procedures and Methods

Patients. Of the eight patients studied, six had the common, low-cardiac-output type of congestive heart failure and two had cor pulmonale. Table 1 presents pertinent information concerning each patient; the type of heart disease, the manifestations and severity of congestive heart failure and the therapy received. Five of the eight patients were so acutely ill that they received, before the first set of measurements, specific medication which probably altered the dynamics of their congestive heart failure. Nevertheless, at the time of the observations all patients were still in obvious congestive heart failure to the degrees indicated, were not improving progressively and, on the basis of clinical evaluation, were judged unlikely to regain cardiac compensation without subsequent digitalization. The first measurements are, therefore, considered valid for the degrees of congestive heart failure indicated.

After these measurements, the patients were given digitalis leaf orally and when cardiac compensation had been achieved the measurements were repeated. The interval between the two studies was two to three weeks in six subjects, five weeks in one subject and six months in the remaining patient. All patients regained a satisfactory degree of cardiac compensation, as judged by their ability to return to their former activities without the recurrence of signs or symptoms of cardiac decompensation. Compensation was maintained in all patients by digitalis leaf taken orally, and diuretics were not required.

Table 1.—*Clinical Cardiovascular Status of Patients Studied and Medication Received (Arranged in Order of Severity of Congestive Heart Failure)*

	Surface Area sq. M.	Date	Weight pounds	Degree of Failure	Signs of Congestive Heart Failure					Medication‖
					Veins	Rales	Liver	Edema	Dyspnea	
F. W.; M, 64		4/28/50	183	4+	4+	3+	3+	4+	3+	None
(ASHD)	1.72	5/19/50	148	0	0	0	0	0	0	Digitalized
J. P.; M, 53		11/10/49	168	4+	3+	3+	4+	3+	3+	Digoxin*
(Unk & ASHD)	1.84	11/29/49	148	0	0	0	1+	0	0	Digitalized
I. B.; F, 52		3/24/50	132	3+	3+	2+	3+	3+	2+	Digoxin†
(RHD)	1.51	4/26/50	111	0	0	0	1+	0	0	Digitalized
R. D.; M, 68		1/13/50	118	3+	0	1+	3+	0	3+	Aminophylline‡
(HHD & ASHD)	1.50	1/31/50	116	0	0	0	0	0	0	Digitalized
L. W.; M, 51		6/14/49	141	3+	2+	1+	3+	1+	2+	Aminophylline§
(HHD)	1.71	6/28/49	132	0	0	0	0	0	0	Digitalized
W. G.; M, 70		7/ 7/49	119	2+	2+	0	2+	2+	0	None
(Unk & ASHD)	1.53	1/20/50	111	0	0	0	0	0	0	Digitalized
W. P.; M, 41		11/ 1/49	157	4+	3+	2+	3+	4+	3+	None
(CP)	1.69	11/22/49	131	0	0	0	0	0	0	Digitalized
J. N.; M, 56		1/27/50	196	1+	0	2+	3+	0	1+	Mercuhydrin¶
(CP)	1.91	2/10/50	185	0	0	0	0	0	0	Digitalized

ASHD, Arteriosclerotic heart disease; RHD, rheumatic heart disease; HHD, hypertensive heart disease; CP, cor pulmonale; Unk, unknown etiology.

* Digoxin 0.5 mg. intravenously 12 hours previously.

† Digoxin 0.5 mg. intravenously four days before; Mercuhydrin 2 ml. and aminophylline 0.48 Gm. intramuscularly five days before.

‡ Aminophylline 0.48 Gm. intramuscularly two days and one day previously.

§ Aminophylline 0.48 Gm. intramuscularly six days and five days previously.

¶ Mercuhydrin 2 ml. intramuscularly three days previously.

‖ Medication tabulated in relation to determinations. Therapy common to all patients—bed rest, low salt diet, sedatives.

TABLE 2.—*Oxygen Consumption, Blood Oxygen Content, Cardiac Output and Blood Volume during Congestive Heart Failure and after Recovery of Cardiac Compensation (Each Value Is Average of Three Periods, Except as Designated)*

Patient	Status†	Ventilation Vol. L./min.	O_2 Consumption ml./min.	Arterial O_2 Content vols.%	Blood O_2 Saturation		A-V Difference vols. %	Cardiac Output L./min.	Cardiac Index L./min./M.²	Plasma Protein Gm. %	Plasma Vol. L.	Hematocrit (arterial) %	Blood Vol. L.
					Arterial %	Mixed Venous %							
"Low Output" Failure													
F. W.	Decomp.	10.36	316	17.8	84	46	8.1	3.9	2.3	7.0	3.3	45	6.0
	Comp.	11.17	251	19.7	90	62	6.3	4.0	2.3	7.1	2.8	52	5.4
J. P.	Decomp.	14.34*	292*	16.3	84	46	7.8	3.8*	2.0*	5.2	4.6	46	8.6
	Comp.	9.49	203	17.6	87	64	4.7	4.4	2.4	6.3	4.0	43	7.0
I. B.	Decomp.	8.95	216	19.2	88	46	9.4	2.3	1.5	5.9	3.2	49	6.1
	Comp.	14.33	341	20.4	95	68	5.8	5.9	3.9	7.5	2.2	48	4.4
R. D.	Decomp.	12.50*	261*	18.4	93	48	9.0*	2.9*	1.9*	6.3	2.9	43	5.2
	Comp.	10.88	261	17.3	90	65	4.7	5.5	3.7	6.7	2.6	38	4.1
L. W.	Decomp.	11.31	262	18.5	97	38	11.2	2.4	1.4	—	3.6	49	7.0
	Comp.	6.63*	218*	20.0	95	64	6.5*	3.4*	2.0*	—	2.3	53	4.9
W. G.	Decomp.	6.96	189	12.6	86	34	7.5	2.5	1.6	6.8	4.4	34	6.6
	Comp.	5.85	179	15.2	91	52	6.4	2.8	1.8	6.3	3.0	35	4.7
Average													
Decompensated		10.72	256	17.1	90	43	8.8	3.0	1.8	6.2	3.7	44	6.6
Compensated		9.72	242	18.4	91	63	5.8	4.3	2.7	6.8	2.8	45	5.2
% change		−9	−5	+7	+2	+46	−35	+46	+49	+8	−23	+2	−22
Cor Pulmonale													
W. P.	Decomp.	8.62	291	18.3	71	50	5.6	5.2	3.1	5.0	3.6	61	9.3
	Comp.	12.30	303	22.8	76	59	5.1	5.9	3.5	7.7	2.2	65	6.4
J. N.	Decomp.	8.12*	317*	22.6	74	53	6.4*	5.0*	2.6*	6.7	2.5	70	8.2
	Comp.	8.35	293	22.5	75	58	4.9	5.9	3.1	7.0	2.7	56	6.2
Average													
Decompensated		8.37	304	20.5	73	51	6.0	5.1	2.8	5.9	3.0	66	8.8
Compensated		10.32	298	22.6	75	59	5.0	5.9	3.3	7.3	2.5	61	6.3
% change		+23	−2	+10	+4	+14	−16	+16	+16	+25	−19	−8	−28

* Average of two periods.

† Decomp. = during congestive heart failure; Comp. = compensated state.

Procedures and Analyses. The following functions were measured by standard technics: cardiac output by the direct Fick method, cardiac and peripheral blood pressures by Hamilton manometers with optical recording, oxygen content of arterial and mixed venous blood by manometric analysis (Van Slyke and Neill), plasma and blood volumes by the Evans blue dye (T-1824) method, renal hemodynamics by inulin and para-aminohippurate clearance technics and electroyte excretions from determination of the blood and urine concentrations of sodium and potassium (flame photometer) and chloride (modified Volhard method). Standard procedures and methods, fully detailed in a previous report,[4] were used to obtain the specimens and tracings, analyze the blood, urine and air samples, measure the pressure tracings and calculate the final values.

All determinations were made in the morning after an overnight fast. Measurements of the above

TABLE 3.—*Intracardiac and Peripheral Blood Pressures, Vascular Resistances and Heart Rate during Congestive Heart Failure and after Recovery of Cardiac Compensation (Each Value Is Average of Three Periods Except as Designated)*

Patient	Status†	Ventricular Rate per min.	Femoral Vein mm. Hg	Right Atrium mm. Hg	Right Ventricle		Pulmonary Artery			Femoral Artery			Systemic "Vascular" Resistances‡	
					Syst. mm. Hg	End Diast. mm. Hg	Syst. mm. Hg	Diast. mm. Hg	Mean mm. Hg	Syst. mm. Hg	Diast. mm. Hg	Mean mm. Hg	"Total" dynes, sec., cm.$^{-5}$	"Arteriolar" dynes, sec., cm.$^{-5}$
"Low Output" Failure														
F. W.	Decomp.	102	—	31	77	30	—	—	—	129	72	87	1793	1150
	Comp.	100	—	2	—	—	—	—	—	153	78	98	1966	1917
J. P.	Decomp.	148	15	—	42	11	41	35	39	114	82	92	1958	1638
	Comp.	86	2	0.5	27	3	27	10	17	132	87	99	1817	1718
I. B.	Decomp.	127	—	17	—	—	—	—	—	141	79	96	3295	2708
	Comp.	61	—	5	—	—	—	—	—	165	65	94	1267	1198
R. D.	Decomp.	110	6	8	—	—	—	—	—	168	98	117	3243	3020
	Comp.	109	5	2	63	7	60	32	42	232	91	120	1740	1693
L. W.	Decomp.	107	19	—	76	23	82	45	58	194	142	157	5350	4698
	Comp.	74	4	—	48	4	52	24	35	220*	123*	155*	3705	3603
W. G.	Decomp.	79	31	—	37	22	35	20	29	133	88	113	3615	2612
	Comp.	63	—	12	34	11	38	16	23	137	77	90	2600	2252
Average														
Decompensated		112	17.7	19.6	52	19	53	33	42	146	93	110	3209	2638
Compensated		82	3.7	3	36	6	39	17	25	173	87	109	2182	2063
% change		−27	−79	−84	−30	−68	−26	−50	−40	+18	−6	−1	−32	−22
Cor Pulmonale														
W. P.	Decomp.	90	—	17	89	31	95	49	68	146	103	124	1913	1650
	Comp.	89	—	0	60	6	—	—	—	166	108	134	1814	1813
J. N.	Decomp.	81	—	5	73	11	75	39	42	160	93	120	1930	1845
	Comp.	76	—	2	48	7	47	22	28	155	71	97	1306	1277
Average														
Decompensated		85	—	11	81	21	85	44	55	153	98	122	1921	1747
Compensated		82	—	1	54	6.5	—	—	—	160	90	116	1560	1545
% change		−4	—	−91	−33	−69	—	—	—	+5	−9	−5	−19	−12

* One period only.

† Decomp. = during congestive failure; Comp. = compensated state.

‡ Resistances to blood flow in systemic circuit

Total = total resistance to flow from aorta through right heart; $R = \frac{FA \times 1332.}{C.O.}$

Arteriolar = Vascular resistance from large arteries to femoral vein; $R = \frac{(FA - FV) \times 1332}{C.O.}$ (where FV was not available RA was substituted).

ix functions were made during each of three successive periods of 15 minutes duration, with the ardiovascular functions measured at the mid-point f the periods and the renal hemodynamic functions and water and electrolyte excretions measured over the entire period, the sampling for blood volume determinations extending over the second and third periods.

TABLE 4.—*Renal Hemodynamics and Water and Electrolyte Excretions during Congestive Heart Failure and after Recovery of Cardiac Compensation (Each Value Is Average of Three Periods, Except as Designated)*

Pat.	Status†	Glomer. Filtrat. Rate. ml./min.	Renal Plasma Flow ml./min.	Filtrat. Frac. %	Renal Blood Flow ml./min.	Renal Fraction %	Renal‡ Vasc. Resist. dynes, sec., cm.$^{-5}$	Urinary Excretions			
								Urine Flow ml./min.	Na μEq./min.	K μEq./min.	Cl μEq./min.
"Low Output" Failure											
F. W.	Decomp.	106	237	45	432	11.1	10,580	2.3	106	57	–
	Comp.	127	363	35	757	19.0	10,140	3.0	199	129	263
J. P.	Decomp.	89	211	42	391	10.4	15,750	1.7	0.5	44	4
	Comp.	147	429	34	753	17.3	10,400	6.4	184	95	191
I. B.	Decomp.	68	132	52	259	11.1	24,400	2.5	70	36	60
	Comp.	114	296	39	575	9.7	12,390	9.3	122	94	124
R. D.	Decomp.	91*	190*	48*	332*	11.5	26,500	0.3	6	31	10
	Comp.	103	287	36	463	8.4	19,850	2.4	367	94	135
L. W.	Decomp.	78	121	64	238	10.1	46,400	0.7	9	30	16
	Comp.	98*	211*	46*	447*	13.3	27,100	0.4	16	24	—
W. G.	Decomp.	54	137	39	207	8.2	31,620	0.8	34	30	42
	Comp.	78	283	28	436	15.7	14,310	5.4	104	84	139
Average											
Decompensated		81	171	48	310	10.4	25,900	1.4	38	38	29
Compensated		111	312	36	572	13.9	15,700	4.5	165	87	147
% change		+37	+82	−25	+85	+34	−39	+222	+344	+129	+407
Cor Pulmonale											
W. P.	Decomp.	94	130	72	334	6.4	25,600	1.1	54	65	91
	Comp.	118	351	34	1003	17.0	10,690	2.2	168	205	130
J. N.	Decomp.	108	279	39	930	18.7	9,900	0.5	21	66	10
	Comp.	157	535	29	1215	20.5	6,250	0.7	20	107	48
Average											
Decompensated		101	204	56	632	12.6	17,750	0.8	38	66	50
Compensated		138	443	32	1109	18.8	8,470	1.5	94	156	89
% change		+37	+117	−43	+76	+49	−52	+88	+147	+136	+78

Blood electrolyte concentrations (Na, K, Cl) were essentially the same on the two occasions except for sodium concentration in J. P.; 114 mEq./L. during decompensation and 133 mEq./L. when compensated.

* Average of two periods.

† Decomp.—during congestive heart failure; Comp.—compensated state.

‡ Resistance of renal vascular tree from renal artery to femoral vein.[5]

RESULTS

The data for each patient are presented in three tables: table 2, cardiac output and blood volumes; table 3, intracardiac and peripheral blood pressures; table 4, renal hemodynamics and water and electrolyte excretions. Each value is the average of the three individual measurements made during the three consecutive periods. The patients have been arranged in the order of the severity of the congestive heart failure, as judged by clinical evaluation.

At the time of the determinations during

TABLE 5.—*Values for Cardiovascular, Renal and Urinary Functions during the Peak Effect of Intravenous Digoxin in Congestive Failure Compared with Values for the Compensated State after Digitalization*

	Patient W. G.		Patient R. D.		Patient I. B.		Patient J. P.	
	Digoxin	Compensated	Digoxin	Compensated	Digoxin	Compensated	Digoxin	Compensated
O_2 Consumption, ml./min.	198	175	298	261	190	341	308	203
Arterial O_2 Content, vols. %	12.2	15.2	17.6	17.3	18.2	20.4	15.0	17.7
Mixed Venous O_2 Content, vols. %	5.9	8.7	11.9	12.5	11.7	14.6	10.8	13.0
A-V O_2 Difference, vols. %	6.3	6.5	5.7	4.7	6.5	5.8	4.2	4.7
Cardiac Output, L./min.	3.2	2.8	5.2	5.5	3.1	5.9	6.7	4.4
Cardiac Index, L./min./sq. m.	2.1	1.8	3.5	3.7	2.0	3.9	3.4	2.4
Right Atrial Pressure, mm. Hg	11	12	0	2	10	5	3	0.5
Femoral Venous Pressure, mm. Hg	12	—	1	5	—	—	5	2
Femoral Artery Pressure,* mm. Hg	161/95 (120)	137/77 (90)	207/101 (146)	232/91 (120)	165/66 (102)	165/65 (94)	123/79 (103)	132/87 (99)
Systemic Arteriolar Resistance, dynes, sec., cm.$^{-5}$	2727	2252	1827	1693	2172	1198	1068	1718
Plasma Volume, L.	4.6	3.0	—	3.6	3.3	2.2	4.6	4.0
Blood Volume, L.	6.3	4.7	—	4.1	6.2	4.4	8.3	7.0
Glomerular Filtration Rate, ml./min.	61	78	105	103	71	114	123	147
Renal Plasma Flow, ml./min.	163	283	236	287	164	296	359	429
Filtrat. Frac. %	38	28	44	36	43	39	34	34
Renal Blood Flow, ml./min.	246	436	407	463	304	575	641	753
Renal Fraction, %	7.7	15.7	7.8	8.4	9.8	9.7	9.7	17.1
Renal Vasc. Resist. dynes, sec., cm.$^{-5}$	31,600	14,310	20,100	19,850	18,100	12,390	12,000	10,400
Urine Flow, ml./min.	2.3	5.4	1.2	2.4	4.6	9.3	5.7	6.4
Na Excretion, μEq./min.	207	104	112	367	254	122	6	184
K Excretion, μEq./min.	57	84	54	94	47	94	118	95
Cl Excretion, μEq./min.	255	139	110	135	—	124	71	191

Values in compensated state are average of three resting periods.
Values for digoxin are single period determinations, 90 to 120 min. after administration of glycoside.
* Value in parenthesis is mean pressure, planimetrically determined.

congestive heart failure four subjects (J. P., I. B., R. D., and W. G.) received intravenously, after the three control periods analyzed in this paper, single therapeutic doses of Digoxin. The immediate cardiovascular and renal effects of these doses of Digoxin have been reported elsewhere.[4] There has been a tendency to consider the acute effects of single, therapeutic doses of cardiac glycosides given during congestive heart failure as comparable to the findings in the compensated state following digitalization. In order to present data on this point the maximum values following intravenous Digoxin were compared with the values in the compensated state in these four patients (table 5).

Discussion

Patients with Low-Cardiac-Output Type of Congestive Heart Failure

The present observations confirm the pattern of changes in cardiovascular and renal functions previously observed by others in congestive heart failure and in the compensated state, and indicate that recovery of cardiac compensation is generally associated with the following changes: an increase in cardiac output, an increase in oxygen content of mixed venous blood, a decreased arteriovenous oxygen difference, a reduction in blood volume, a reduction in blood pressures in the vessels behind the previously failing ventricles, a fall in the residual pressures within these ventricles, an unchanged mean pressure but increased pulse pressure in the systemic arteries, a reduction in vascular resistance in the systemic and pulmonic vascular beds, an improvement in renal plasma (and blood) flow and glomerular filtration rate, and an increase in the excretion of water and electrolytes. These changes were qualitatively similar from patient to patient. Occasionally, however, no change, or a change in a different direction from the group effect, was encountered for some function in an individual subject. Quantitatively, the *degree of change* and the *final value* varied widely among the subjects for practically all functions measured. Although this variation appears to exclude a definitive pattern in the quantitative aspects of the recovery process from cardiac decompensation, an analysis of the changes in individual functions reveals pertinent information concerning the failing and recovering circulations.

Cardiac Output, Blood Oxygen Content, Oxygen Consumption (*table 2*). With the recovery of compensation, cardiac output rose by 0.1 liter per minute (no change) to 3.6 liters per minute, representing increases of 3 to 155 per cent (average 46 per cent) above the values during congestive heart failure. The variability of the increases was striking. In one patient (F. W.) the cardiac output did not change, in another patient (W. G.) the increase was equivocal (0.3 liter per minute) and only in two patients (I. B. and R. D.) did cardiac output rise to values considered to be normal.

The changes in cardiac output probably do not indicate the degree of improvement in cardiovascular function. Viewed from the standpoint of the total utilization of oxygen and its transport by the blood stream, the circulation appeared to improve decidedly in all patients as compensation was attained. Thus, in five subjects the mixed venous oxygen saturation returned to normal values, while the arteriovenous oxygen difference became normal in three patients and just exceeded the normal limit of 6 volumes per cent in the other three (6.3, 6.5, 6.4 volumes per cent). In subject F. W., the discrepancy between the failure of cardiac output to increase upon recovery of compensation while the arteriovenous oxygen difference decreased, may be explained by an associated decrease in oxygen consumption, which had been elevated during congestive failure. Such an explanation appears untenable in patient W. G., in whom oxygen consumption remained the same as cardiac output rose equivocally and arteriovenous oxygen difference fell decisively.

A comparison in these six patients of the oxygen consumption during the two states of cardiac competence showed a higher consumption during congestive failure than in the compensated state in three patients, the same values on both occasions in two patients and lower values during failure in the remaining patient.

The present data substantiate the well docu-

mented observation that cardiac output is a rather variable index of the adequacy of cardiovascular function, whereas the arteriovenous oxygen difference, relating output to demand, is a more stable and reliable index. Finally, a comparison of the cardiac indices during decompensation and compensation indicates that the level of cardiac output is not the determinant of congestive heart failure and that there are no specific levels of cardiac output at which congestive failure will necessarily occur or necessarily disappear.

*Blood Volume** (*Table 2*). Blood volume usually decreased as cardiac compensation returned and the decrease in total volume was shared by comparable decreases in plasma and red cell volumes. Plasma volume fell in all subjects by 0.5 to 1.3 liters, average 0.8 liters (−23 per cent). Concomitantly, plasma protein concentration increased, but inconsistently and without relation to the decrease in plasma volume. In five of the six subjects, total blood volume fell by 1 to 2 liters, average 1.75 liters (−26 per cent). In subject F. W., total blood volume did not change, even though his weight (edema) loss of 35 pounds was the largest for the group. Further evidence of a lack of relationship between decrease in blood volume and loss of edema is indicated by subject R. D. who lost but two pounds in weight yet sustained a sizable decrease of 1 liter (−20 per cent) in blood volume. In all subjects the blood volume in the compensated state was within normal values.

Intracardiac Pressures (*Table 3*). One of the most consistent changes upon recovery from congestive failure was the return to normal of the residual pressures on the right side of the circulation, that is, in and behind the right ventricle. Right ventricular end diastolic pressure, right atrial pressure and femoral venous pressure fell from elevated levels to normal in all but one of the instances where these measurements were made. In patient W. G., right ventricular end diastolic pressure and right atrial pressure fell as in the other five patients, but still remained elevated (11 to 12 mm. Hg). Physical findings and right atrial pressure tracings suggest that this patient had tricuspid insufficiency.

Pulmonary "capillary" (left atrial) pressure was not measured and hence changes in the residual pressures behind the left ventricle were not determined. Some index to the behavior of these pressures may be surmised from the changes in pulmonary artery pressures. Only in one (J. P.) of the four patients in whom such measurements were made did pulmonary pressures fall to normal values. In the other three patients, pulmonary artery systolic, diastolic and mean pressures remained decidedly elevated in two (R. D., L. W.) and slightly elevated in the third (W. G.). Since these patients did not have pulmonary disease, which might have increased pulmonary vascular resistance, their increased pulmonary pressures may well have resulted from residual vascular engorgement behind the left ventricle. In this respect it may be significant that systemic hypertension was the etiologic factor responsible for the congestive failure in the two patients (R. D., L. W.) in whom the highest pulmonary pressures persisted after compensation returned. Furthermore, both patients had marked symptoms and signs attributable to pulmonary congestion during their congestive heart failure. Perhaps, because of the persistent load of the hypertension upon the left ventricle, its recovery was less complete than the recovery of the right ventricle and lead to some residual pulmonary engorgement in these patients even after the disappearance of signs of right ventricular failure.

Systemic Arterial Pressure and Vascular Resistance (*Table 3*). In the systemic arteries the principal pressure change associated with the recovery of compensation was an increase in pulse pressure, due largely to a consistent rise in systolic pressure and only slightly to a small and inconsistent fall in diastolic pressure. Mean arterial pressure remained relatively unchanged. Since total blood flow (cardiac output) was considerably greater in the compensated state than during congestive heart failure while the pressure head (mean arterial pressure) remained unchanged, it follows that the *total resistance* to blood flow in the systemic circuit

* The shortcomings of the T-1824 method of determination of blood volume and its partitions render conclusions based on this method tentative at best.

decreased as compensation returned. This was observed in five subjects; in the sixth (F. W.), the total resistance increased slightly.

A consideration of the resistance to blood flow indicates that the observed decrease in total resistance upon recompensation was not solely the result of the customary dilatation of a vasoconstricted arteriolar bed. Thus, systemic *arteriolar vascular resistance* decreased in only three of the six subjects, remained unchanged in two and apparently increased in one. Furthermore, in those instances where arteriolar resistance fell, its decrease was less than the decrease in total resistance. It follows, then, that during cardiac decompensation significantly increased resistance to blood flow may be offered by the circulatory system beyond the arterioles, probably by the failing right heart and secondarily thereto, by the increased pressure in the engorged systemic venous bed. In some patients this resistance appears to be considerable and contributes sizably to the total resistance to blood flow. In patient F. W., whose right atrial pressure during congestive heart failure was unusually high (31 mm. Hg), this cardiac and engorged venous resistance constituted one-third of the total resistance to blood flow and the arteriolar bed actually appeared to be dilated, as indicated by the increase in arteriolar resistance as compensation returned. On all occasions, however, arteriolar vascular resistance still constituted quantitatively the major resistance to systemic blood flow. In short, in congestive heart failure the *increase* in total resistance to systemic blood flow is only partly, and inconstantly, due to the usual mechanism of arteriolar vasoconstriction, the failing right heart and engorged venous tree consistently contribute to the increased total resistance and in some instances markedly so.

Renal Hemodynamic Functions (*Table 4*). With recovery of cardiac compensation renal hemodynamics returned toward normal. Renal blood flow and glomerular filtration rate increased in all six subjects. The average increase in renal plasma flow (+82 per cent) and renal blood flow (+85 per cent) was considerably greater than the average increase in glomerular filtration rate (+37 per cent). However, these percentage figures merely reflect the repeated observation that in congestive heart failure renal blood flow is decreased disproportionately more than glomerular filtration, with the result that relatively small increments in blood flow represent large percentage increases. Such figures obscure the important fact that in no instance did renal blood flow approach normal values, whereas filtration rate became normal in three patients (F. W., J. P., I. B.) and nearly normal in a fourth (R. D.). In the other two patients glomerular filtration remained moderately depressed. Filtration fraction fell in all patients but still remained well above normal in each instance. In spite of the definite improvement, renal hemodynamic functions in the compensated state still showed a residual abnormality similar to that during cardiac decompensation, namely, blood flow reduced disproportionately more than glomerular filtration, which at times was normal.

Total renal vascular resistance was uniformly increased during congestive heart failure and decreased with the return of compensation in all patients except F. W., in whom there was no change. Calculations according to the method of Gómez[5] indicate that during cardiac decompensation a considerable portion of the increase in resistance to renal blood flow is located in the renal venous segment. This is analogous to the partition of resistance to blood flow in the total systemic circulation.

Renal fraction (per cent of cardiac output perfusing the kidney) increased in four subjects and decreased in the other two. In only three subjects did the final value approximate the normal of 18 per cent; F. W. 19 per cent, J. P. 17 per cent and W. G. 16 per cent. Furthermore, the increase in renal blood flow was not directly related to the increase in the cardiac output. For example, in patient W. G. renal blood flow increased by 229 ml. per minute and renal fraction doubled, (8 to 16 per cent) whereas cardiac output increased by only 0.3 liter per minute, from 2.5 to 2.8 liters per minute. In contrast, in patient R. D. renal blood flow increased by only 131 ml. per minute and renal fraction fell (11.5 to 8.5 per cent) while cardiac output increased by 2.6 liters per minute, from 2.9 to 5.5 liters per minute.

Electrolyte and Water Excretion (*Table 4*). The basal rate of electrolyte excretion consistently increased as cardiac compensation returned. In terms of average values, sodium excretion quadrupled, potassium excretion doubled and chloride excretion quintupled. Urine flow tripled. Only in three instances did the response in electrolyte excretions vary from the group response, twice sodium excretion and once potassium excretion remained unchanged. In no instance did electrolyte excretion decrease. Since the food, water and electrolyte intakes were not controlled or measured, the significance of these increased electrolyte excretions obviously cannot be assessed, particularly in relation to the changes in renal or cardiovascular dynamics. Nevertheless, it is of interest that the increases in electrolyte and water excretions were unrelated to the degree of improvement, or the final values attained, in either glomerular filtration rate, renal plasma flow or cardiac output.

Comparison of Compensated State with Response to Intravenous Digoxin (*Table 5*). There was considerable similarity between the cardiovascular dynamics at the peak of the intravenous Digoxin response and in the compensated state, whereas the renal effects showed additional improvement as full compensation returned. The various blood pressures and the arteriovenous oxygen differences were comparable on the two occasions. The cardiac outputs, however, were more variable and the two sets of determinations show differences from subject to subject, both in the extent of the changes and their direction. As expected, blood volume remained unchanged during the acute action of Digoxin and fell with subsequent compensation. Both renal plasma flow and glomerular filtration rate were consistently higher in the compensated state than during the Digoxin response and a similar, though less consistent, effect occurred in electrolyte and water excretion. Since renal function improved while cardiovascular dynamics remained unaltered, it is at least possible that the additional improvement in these renal functions may have been secondary to the improved cardiovascular status.

Patients with Cor Pulmonale and Congestive Heart Failure

As these two patients recovered cardiac compensation the changes in their cardiovascular and renal functions were similar to those observed in the patients with "low-output" type of congestive heart failure, with the following differences: (1) certain cardiovascular functions, notably cardiac output, arteriovenous oxygen difference and systemic vascular resistance, showed less marked improvement, perhaps because their original deviations from normal were not as marked; (2) several important functions returned to normal, particularly cardiac output, arteriovenous oxygen difference, glomerular filtration rate, renal blood flow and renal fraction; (3) abnormal values persisted for determinations dependent on abnormal pulmonary function, namely, arterial oxygen unsaturation, elevated hematocrit and increased pulmonary artery pressures.

In both patients, cardiac output and arteriovenous oxygen difference were in the normal range during congestive heart failure. With recovery, the increase in cardiac output (average +16 per cent), the rise in mixed venous oxygen saturation (average +18 per cent) and the fall in arteriovenous oxygen difference (average −16 per cent) imply that the "normal" values during congestive failure were in fact not normal for these subjects, for improvement occurred as compensation was attained (table 2).

Arterial oxygen saturation did not change materially and remained at approximately 75 per cent. In spite of the persistence of the hypoxia blood volume decreased (table 2). In one patient the decrease of 2 liters was due entirely to loss of red cell volume; in the other patient the decrease of 3 liters was shared equally by plasma and red cells.

The changes in the various blood pressures (table 3) were qualitatively similar to those already described, except that pulmonary artery pressures and right ventricular systolic pressure remained elevated. In both subjects, mean right atrial pressure fell to normal, whereas right ventricular end diastolic pressure remained somewhat elevated (6 and 7 mm. Hg),

perhaps an indication that complete recovery from right ventricular failure had not been attained.

The changes in renal and urinary functions (table 4) were similar, but apparently more marked than in the patients with "low-output" congestive failure. The final value for glomerular filtration rate, renal blood flow, renal fraction, renal vascular resistance and electrolyte excretions returned to normal levels. Filtration fraction fell but still remained above normal, apparently a function of the high hematocrit since renal plasma flow remained low, even though renal blood flow became normal.

General Considerations

Because of the variations in response among the patients studied it is not possible to derive a definitive pattern of quantitative relationships between the cardiovascular and renal functions in the recovery process from congestive heart failure. The extent of the variations may have depended, perhaps to a pertinent degree, upon differences in the initial abnormality for each function and these in turn upon differences in the stages of the heart disease of the individual subjects. Such differences may have obscured fundamental relationships between the changes in the various functions, particularly in this small group of subjects. The significance of the observations in these few patients appears to be that they define at least a minimal spread in the cardiovascular and renal changes associated with recovery of cardiac compensation. Moreover, the marked differences in the individual responses suggest that similar results might be anticipated in a larger series of patients. More pertinent, perhaps, any theory concerning the dynamics of recovery from congestive heart failure should account for the varied changes in cardiovascular and renal function here observed.

The present observations indicate that recovery of cardiac compensation from congestive heart failure is generally associated with an improvement *toward normal* in cardiovascular and renal function. The extent of the changes and the approximation of the normal varies considerably for the different functions from patient to patient and even in the same patient. Moreover, important functions do not return *to normal* and indeed may show no change whatever in individual patients. Several functions, which appear to depend on other more primary functions, consistently become normal. In this category belong blood volume, residual pressures in the large veins and right heart and the excretion of electrolytes and water. A similar return to normal need not, and often does not, occur in such more primary functions, as cardiac output, renal plasma and blood flow and filtration fraction, while arteriovenous oxygen difference and glomerular filtration rate may become normal in some patients and not in others. Finally, neither in the degree of improvement nor in the final values attained does a consistent relationship emerge between the changes in the functions here measured, particularly the more primary functions.

Recovery of cardiac compensation appears not to be contingent upon a given degree of improvement in any one or any combination of the primary cardiovascular-renal functions here measured, nor does compensation appear to require the attainment of normal values for these functions. The compensated state is not, therefore, a normal state from the standpoint of cardiovascular and renal functions. Though often improved, these functions tend to remain residually altered in the direction of the abnormal pattern present in congestive heart failure, at least in the compensated state of the first month after recovery from cardiac decompensation. Follow-up studies are required to determine whether further improvement and normal functions return as compensation, with adequate therapy, is maintained for long periods of time.

Finally, an extension of such long term, repeated studies of the changes in cardiovascular and renal dynamics in the same patients *throughout the course* of their heart disease are necessary to clarify the pathologic physiology of congestive heart failure. Such observations are at present lacking.

Summary

1. Simultaneous determinations were made of several cardiovascular and renal functions in six patients with "low-output" heart failure and in two patients with cor pulmonale, during congestive heart failure and after compensation had been regained. Determinations were made of the following functions: cardiac output, oxygen content of arterial and mixed venous blood, peripheral and intracardiac blood pressures, blood volume, renal hemodynamics and electrolyte and water excretion.

2. With recovery of cardiac compensation these functions tended to improve toward normal but considerable variation was noted between subjects, both in the degree of change in the different functions and in their approach to normal values. The changes in the patients with cor pulmonale were similar to those in the patients with "low-output" failure, except for functions dependent on the pulmonary disease.

3. Several functions of a more secondary nature (blood volume, excretion of electrolytes and water, residual pressures in the large veins and right heart) returned to normal, whereas important more primary functions (cardiac output, arteriovenous oxygen difference, renal plasma flow, glomerular filtration rate) frequently did not become normal, although they generally improved. The final cardiovascular and renal functions often presented an abnormal pattern similar to, but not as marked as, that originally present during congestive heart failure.

4. No consistent relationship in degree of improvement nor in the final values attained was apparent between the functions measured, particularly in the more primary functions.

5. Recovery of satisfactory and seemingly equal degrees of cardiac compensation appeared not to be contingent upon the degree of improvement or the final value attained in any one or any combination of the more primary functions measured.

6. The considerable variations in response between subjects and functions may have been due to the different stages of heart disease at the time of the initial observations and these differences may have obscured fundamental interrelationships not apparent in the few patients studied.

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Sumario Español

Mayormente basado en observaciones cuidadosas en pacientes cardíacos durante decompensación cardíaca y en pacientes controles no cardíacos, dos suposiciones se han propuesto: (a) que la decompensación cardíaca se desarrolla como las funciones cardiovasculares y renales cambian del tipo hallado en sujetos controlles al tipo hallado en pacientes decompensados, y (b) que el retorno a, o, hacia lo normal ocurre en estas funciones según la compensación cardíaca se recobra. Que estas suposiciones no son necesariamente válidas se indica por las determinaciones aquí reportadas de dinámicas cardiovasculares, funciones renales, volumenes de sangre y excreciones de electrólitos en ocho pacientes durante decompensación cardíaca y luego de recobro de la compensación.

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Plasma Electrolyte Concentrations in Ambulatory Cardiac Patients

By NEAL S. BRICKER, M.D., AND LAURENCE G. WESSON, JR., M.D.

The authors find that electrolyte concentrations of the plasma of the more severely ill cardiac patients attending two outpatient clinics are statistically indistinguishable from controls. They note, however, a slight tendency to metabolic alkalosis and occasionally a mild hyponatremia. No instance of "low salt syndrome" was found.

THE EXISTENCE of abnormal concentrations of plasma electrolytes in many patients with chronic congestive heart failure has long been recognized. In particular the plasma sodium concentration is frequently depressed and the plasma bicarbonate concentration either elevated or depressed with the chloride moving reciprocally to the bicarbonate. Two papers[1, 2] have shown that these abnormalities are virtually absent in *untreated*, hospitalized patients.* By implication, treatment is the factor, additional to complications attendant upon impaired cardiac function, which results in hyponatremia and acidosis or alkalosis. The effect of acidifying salts tending to produce metabolic acidosis appears evident, and, if we accept, hypothetically, a tendency of mercurial diuretics to promote the excretion of a bicarbonate-free chloride-rich urine, then the production of metabolic alkalosis by mercurials is understandable. The correlation between hyponatremia and measures designed to effect sodium depletion appears to be close, although the physiologic mechanisms involved in the production of the hyponatremia have not yet been elucidated.

It is the aim of the present paper to delineate further the group of patients with congestive heart failure within which these plasma electrolyte abnormalities occur. Previous studies have dealt with hospitalized patients. Hospitalized patients are heavily weighted, statistically, in two directions: they represent the most severely ill; and they are the most intensively treated. The patients upon whom studies are presented in this paper were drawn entirely from outpatient clinics. All were capable of limited ambulation. Electrolyte abnormalities occurred but they were few and relatively small. From this we conclude that the severity of heart disease consistent with nonhospitalization, when combined with the intensity of edema control measures attainable in an outpatient clinic, is insufficient to produce electrolyte abnormalities of the degree observed frequently in hospitalized patients. The details of this study are recorded below.

MATERIAL AND METHODS

Patients were selected from two hospital outpatient cardiac clinics between February and June, inclusive, 1952.† The group is not representative of the clinic population, since the more seriously ill and more intensively treated were preferentially selected. A cardiovascular history and physical examination was taken on each patient as a basis for cardiac classification. The principle cardiac diagnoses were arteriosclerotic heart disease in 55 per cent, rheumatic heart disease in 23 per cent, hypertensive heart disease in 13 per cent, with 9 per cent miscellaneous. In addition, each patient was questioned for dietary salt intake and for the occurrence of symptoms of the "low salt syndrome." A single, heparinized venous specimen was drawn for determination of plasma sodium, potassium, chloride, bicarbonate and creatinine. On a few patients, two

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* These papers may conveniently be consulted, for careful reviews of the literature on this subject.

† The 4th Medical Division, Bellevue Hospital, and the University Hospital New York University-Bellevue Medical Center.

TABLE 1.—*Statistical Data on 91 Ambulatory Cardiac Patients Grouped According to Intensity and Principal Method of Edema Control. (See Text for Detailed Description)*

Group	Cardiac Classification*	Men Women	Age	Plasma Concentration†				Creatinine
				Sodium	Potassium	Chloride	Bicarbonate	
	Per cent		*Mean*	*mM. per liter*				*mg. per 100 ml.*
Control	IIB—37 IIIC, D—40	28/14	61	141 ± 4	4.3 ± 0.2	106 ± 4	25 ± 2	1.04 ± 0.12
Low salt	IIB—25 IIIC, D—63	11/4	63	139 ± 4	4.4 ± 0.3	107 ± 5	24 ± 4	1.17 ± 0.21
Mercurial	IIIC, D—90	9/0	63	143 ± 5	4.3 ± 0.4	105 ± 4	27 ± 3	1.24 ± 0.39
Low salt-mercurial	IIIC, D—100	12/13	60	142 ± 5	4.4 ± 0.4	108 ± 6	25 ± 5	1.32 ± 0.50

* Miscellaneous classifications are omitted.

† Means and standard deviations for all determinations within each group.

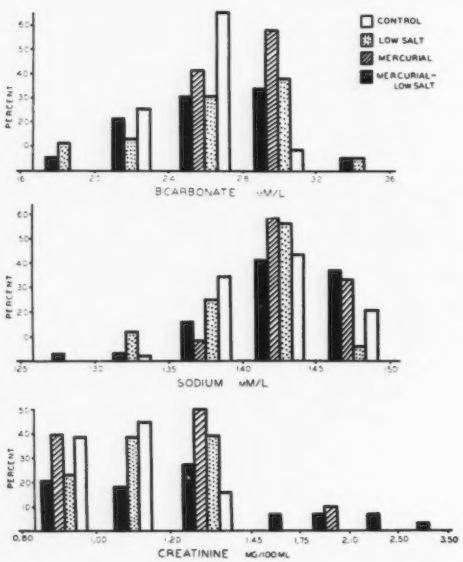

FIG. 1. Frequency distribution of plasma sodium, bicarbonate and creatinine concentrations in ambulatory cardiac patients. The patients are divided into four groups according to the predominant type of treatment. See text for details.

or three additional specimens were drawn on return visits to the clinic.

Patients were classified in four groups according to the amount of dietary salt restriction and the frequency of mercurial (Mercuhydrin) injections. Group I (*control*) received a mercurial injection once weekly or less often, and salt restriction was limited to dispensing with salt at the table. Group II (*low salt*) received a mercurial as in group I, but salt restriction was more intensive. Salt was omitted from cooking and the diet emphasized low-salt or salt-free foods. Group III (*mercurial*) received 2 cc. injections of Mercuhydrin intramuscularly twice weekly or oftener, but salt restriction was no more intensive than in group I. Group IV (*mercurial-low salt*) restricted dietary salt as in group II and received mercurial injections as in group III. A few patients in all groups were taking 2 or 3 Gm. of ammonium chloride daily, but the effect of this dose was not evident in their chloride or bicarbonate values. Additional data on these four groups is summarized in table 1.

Sodium and potassium were determined on a Barclay flame photometer, using an internal lithium standard; bicarbonate, as the carbon dioxide content of air-equilibrated plasma, by the method of Van Slyke and Neill[3]; chloride by the method of Van Slyke and Hiller[4]; creatinine by the method of Bonsnes and Taussky.[5]

OBSERVATIONS

The mean values of the plasma sodium, potassium, chloride, bicarbonate and creatinine for each group are given in table 1. In none of the groups do these values differ significantly from those of the controls. The proportionate distribution of plasma sodium, bicarbonate and creatinine values within each group is illustrated in figure 1. Although the "treatment" groups are far too small to give smooth distribution curves, it is evident that they differ from the control in the following respects. Plasma bicarbonate is frequently elevated, but no more frequently in the mercurial groups than in the low salt group. An elevated plasma

creatinine, suggesting a depressed rate of renal glomerular filtration, was observed frequently in the groups receiving mercurial diuretics. No correlation could be observed, however, between plasma creatinine and the presence or degree of edema. One patient in the mercurial-low salt group was hyponatremic. On two successive clinic visits, her plasma sodium was 130 and 127 mEq. per liter; she had marked edema of the legs and her plasma creatinine was 2.1 mg. per 100 ml. However, she had no symptoms consistent with a "low salt syndrome."

Many patients reported leg cramps and occasionally nausea following the injections of the mercurial diuretics, but these reports could not be correlated with any abnormality of plasma electrolyte or creatinine.

Plasma chloride showed a slightly greater incidence of low values in the "treatment" groups compared with the controls. The distribution of plasma potassium values was the same in all groups.

Conclusions

It is concluded that electrolyte abnormalities occur in ambulatory, nonhospitalized cardiac patients but that such abnormalities are probably less frequent and less marked than among hospitalized patients. The data give no information regarding the relationship of treatment to electrolyte disturbances since all patients with congestive heart failure of more than a few months' duration were receiving therapy.

Sumario Español

Los autores encuentran que las concentraciones de electrolítos en los pacientes cardíacos más enfermos en dos clínicas para pacientes ambulatorios son estadísticamente idénticas a las de controles. Notaron sinembargo una ligera tendencia a alkalosis metabólica y ocasionalmente una leve hiponatremia. Ningún caso del síndrome de deficiencia de sal se encontró.

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The Measurement of Liver Circulation by Means of the Colloid Disappearance Rate

I. Liver Blood Flow in Normal Young Men

By Ernest L. Dobson, Ph.D., George F. Warner, M.D., Caroline R. Finney, A.B., and Muriel E. Johnston, M.A.

A method for calculating the liver blood flow by means of the rate of disappearance of colloidal chromic phosphate from the blood has been reviewed. This method has been applied to the study of liver circulation in a group of 29 fasting normal men. The significance of the colloid disappearance rate constant as a physiologic expression of the liver blood flow has been discussed and the average value obtained for this constant in normal young men was 0.287 ± 0.007 min.$^{-1}$ Extra hepatic colloid localization, hepatic efficiency for colloid removal, speed of mixing, and type and time of sampling have been discussed.

UNTIL RECENTLY the measurement of the circulation of blood through the liver in humans has been hampered by technical difficulty. The impetus given by the advent of intravascular catheterization has aided the problem of liver circulation measurement, and this technic in conjunction with bromsulfalein and urea excretion has been utilized extensively by Bradley and coworkers,[1, 2] by Myers,[3] and by Sherlock and associates.[4]

Simplification of the measurement of liver circulation is afforded by a method developed in this laboratory by which the rate of disappearance of colloid is determined.

Method

A complete discussion of this method has been given elsewhere by Dobson and Jones.[5] Briefly, however, the method consists of measuring the removal rate of colloid particulate matter from the blood stream by the phagocytes of the liver and spleen. In the present study, the disappearance rate of colloidal chromic phosphate labelled with the radioisotope P^{32} was measured in a group of fasting, normal young men. Following the intravenous injection of 5.0 ml. of colloidal chromic phosphate containing 2 to 4 microcuries* of P^{32}, 5.0 ml. serial blood samples (arterial, venous, or both) were taken at frequent intervals. Simultaneous blood volume measurements were made by adding 17 mg. of the blue dye T-1824 to the injection. After collection of the samples, the P^{32} activity of 2.0 ml. aliquots of whole blood was determined with a Geiger-Müller counter. The T-1824 concentration was determined spectrophotometrically in the plasma of the remaining 3.0 ml. of the samples.

Calculations

The colloid concentration of the samples is measured by the incorporated P^{32} activity. When this is plotted on semilogarithmic paper as a function of time, a curve is obtained whose initial portion, following a rapid rise due to mixing, is straight. The duration of the straight portion varies between 5 and 10 minutes (fig. 1). This initial portion of the multicomponent exponential curve closely approximates

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* The amount of radioactivity injected is well within the safe tracer dose range. Four microcuries of P^{32} distributed in a liver of average size will give an initial dose rate of 0.1 r per day and a total cumulative dose of 2 roentgens. The radiation received from the fluoroscopy during a hepatic catheterization is of the order of 10 times greater than that received from the labelled chromic phosphate.

a simple exponential which may be represented by the equation $C = C_o e^{-kt}$ where C is the concentration at any time t, C_o is the initial concentration and k is a constant. The slope of this straight line represents the fraction of the total blood volume perfusing the liver per unit time, and has been termed the colloid disappearance-rate constant, identical with

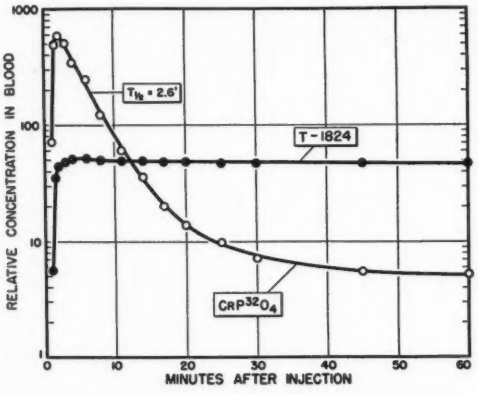

FIG. 1. *Simultaneous Time-Concentration Curves for Chromic Phosphate and T-1824 in Venous Blood.* Following the mixing period the chromic phosphate disappearance curve shows an initial portion which is quite straight for about 10 minutes. The extent of mixing at any time may be gauged by the T-1824 curve. Subject RIC.

k in the equation above.[5] The disappearance-rate constant is related to the half-time of disappearance by the expression, $k = \frac{0.693}{t_{\frac{1}{2}}}$. The liver blood flow in liters per minute may be obtained by multiplying the blood volume by k.

Assumptions

The use of this method for the accurate determination of liver blood flow involves four important assumptions:

1. *Specific Localization.* It is assumed in normal humans that the injected colloidal material localized specifically in the reticulo-endothelial cells of the liver and spleen. Since the liver and spleen are in series with each other, relative distribution between these two organs does not affect the calculations.[5] Extra splenohepatic localizations in other species, that is, dog, rabbit, mouse, and chicken, have been found to be quite low, amounting to about 10 per cent.[5, 6]

2. *Efficiency of Removal.* It is assumed that the colloid particulate matter is removed by the liver and spleen with a high degree of efficiency in a single passage. This has been

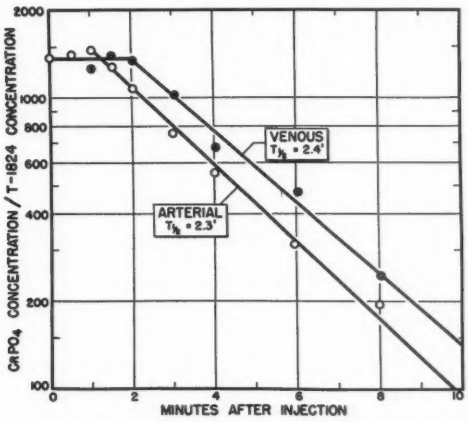

FIG. 2. *Comparison of the ($CrPO_4$–T-1824) Ratio Curves from Arterial and Venous Blood Samples.* Both arterial and venous ratios are plotted as a function of time. The venous curve is derived from the same data as are presented in figure 1. The use of the ratio simply amounts to increasing the first venous sample in figure 1 by a factor of 9, the second sample by 43 per cent and the third sample by 12 per cent as the extent of dilution of the dye indicates.

The arterial disappearance curve (omitted from fig. 1) had an initial slope of 2.1 minutes. Note that the use of the ratio has brought the arterial and venous half-times into nearly perfect agreement. Subject RIC.

shown to be true in the mammalian species mentioned above. The method of preparation of the colloid results in a heterogeneous mixture of particle sizes. Very small particles, amounting to about 0.5 per cent of the total P^{32} activity injected, have been shown to be responsible for the tail portion of the disappearance curve which follows the initial straight line portion (fig. 1). Although the liver is highly efficient in removing large particles, it presumably is poorly efficient in removing these very small particles. The over-all efficiency is probably about 90 per cent.[5]

3. *Use of Initial Straight Portion of the Curve.* Although the complete curve has been shown to be a multicomponent exponential one,[5] disregarding the slower components and simply using the initial slope produces only a small error. This is true because of the small contribution made by these slower components produced by the small-sized particles.

4. *Mixing.* The correct interpretation of the colloid disappearance curve as a measure of liver circulation requires that mixing of the injected material within the circulating blood volume be essentially complete before samples are used for such measurement. Mixing times have been determined from the simultaneous use of T-1824 with the chromic phosphate injection. Early points before mixing is complete are then disregarded when the disappearance slope is determined. Dye levels which have risen to within 10 per cent of the final equilibrium value indicate that the label has mixed with 90 per cent of the circulating blood. This extent of mixing was accepted as complete. Although this criterion of mixing was usually reached in two minutes (fig. 1), a few of the mixing times were prolonged to between 5

TABLE 1.—*Liver Blood Flow Data from 29 Fasting Normal Men*

Subject	Age Yrs.	Weight Kg.	Height Meters	Rate of Disappearance of $CrPO_4$ from Venous Blood		Rate of Disappearance of $CrPO_4$ from Venous Blood Expressed as the Ratio $CrPO_4$/T-1824		Blood Vol. T-1824	
				$t_{\frac{1}{2}}$ min	k min^{-1}	$t_{\frac{1}{2}}$ min	k min^{-1}	Liters	Per cent of Body weight
HUR	21	81.8	1.86	3.0	0 231	2.8	0.248	6.9	8.4
SCH	22	100.0	1.79	2.6	0.267	2.6	0.267	6.3	6.3
ELD	21	76.8	1.90	2.4	0.289	2.3	0.302	6.5	8.5
HER	21	88.7	1.90	2.3	0.302	2.2	0.315	6.2	7.1
SAN	23	74.5	1.84	2.5	0.278	2.3	0.302	6.2	8.4
JON	25	69.6	1.86	3.0	0.231	2.6	0.267	7.7	11.0
CHA	26	67.8	1.78	2.4	0.289	2.4	0.289	5.6	8.2
RIC	20	76.8	1.78	2.6	0.267	2.4	0.289	7.0	9.0
KIR	22	68.2	1.74	2.4	0.289	2.2	0.315	5.1	7.5
LIE	22	91.0	2.20	2.8	0.248	2.8	0.248	8.1	8.9
BID	23	68.3	1.75	2.6	0.267	2.6	0.267	6.7	9.8
COR	26	75.5	1.71	2.8	0.248	2.8	0.248	5.4	7.2
SAV	23	78.9	1.84	2.7	0.257	2.7	0.257	8.2	10.8
LIS	22	72.7	1.89	3.4	0.204	3.4	0.204	7.3	10.0
NEE	23	70.5	1.84	2.3	0.302	2.2	0.315	4.6	6.6
PAC	22	63.6	1.89	2.2	0.315	2.6	0.267	6.3	9.9
MER	23	68.2	1.79	2.9	0.239	2.7	0.257	6.7	9.9
STE	23	61.9	1.77	1.9	0.365	2.2	0.315	7.4	11.9
JOH	22	83.8	1.91	2.7	0.257	2.5	0.278	6.8	8.2
SCH	22	80.5	1.86	2.9	0.239	2.7	0.257	7.0	8.7
CAR	21	77.7	1.80	2.4	0.289	2.4	0.289	6.5	8.4
LAM	21	81.5	1.89	2.6	0.267	2.6	0.267	7.1	8.7
MEL	23	71.5	1.72	2.3	0.302	2.1	0.330	5.2	7.3
WIL	22	77.8	1.81	3.2	0.220	3.0	0.227	6.5	8.4
KAP	22	68.5	1.76	2.2	0.315	2.1	0.330	5.3	7.8
DUH	24	85.7	1.83	2.3	0.302	2.2	0.315	6.5	7.5
COR	26	69.5	1.71	1.8	0.385	1.8	0.385	5.0	7.3
JON	25	70.9	1.89	3.1	0.224	2.8	0.248	6.6	9.4
LIE	20	82.7	1.89	1.8	0.385	2.2	0.315	7.5	9.0
Average				2.50 ± 0.07*	0.282 ± 0.008	2.44 ± 0.06	0.287 ± 0.007		8.5

* All errors are expressed as standard error of the mean.

and 10 minutes. Greatly prolonged mixing times may introduce serious difficulty in determining the initial slope.

An attempt has been made to correct for mixing influences by expressing the sample data as a ratio of chromic phosphate concentration to T-1824 concentration. When points are plotted using this ratio, a curve is obtained in which the rapid rise due to mixing is eliminated (fig. 2). The general features of this ratio curve are: (1) an initial horizontal portion which represents a lag period between the time of injection and the time of arrival at the sampling site of labelled blood which has perfused the liver; and (2) a logarithmic slope which is equivalent to the straight portion of the plain chromic phosphate disappearance curve previously described (fig. 1).

Results

Chromic phosphate disappearance curves and simultaneous T-1824 mixing curves have been obtained in 29 normal, fasting young men. Venous samples were obtained in all, and in five subjects simultaneous arterial samples were taken. The data from venous sampling are presented in table 1. The values for the disappearance slope have been expressed both as half-time and as k, where $k = \frac{0.693}{t\frac{1}{2}}$. The blood volume as measured with T-1824 is expressed both as liters and as per cent of the body weight.

Discussion

The average value for k derived from the disappearance of chromic phosphate from venous blood is 0.282 ± 0.008 minute^{-1}. When mixing influences are corrected for by the use of the ratio $CrPO_4$/T-1824, the average value for k is 0.287 ± 0.007 minute^{-1}. From the close agreement between these two values it appears that mixing errors are minimal in the normal individual. However, in patients with deficient mixing the use of the dye or some other agent as an indicator of mixing is imperative.

From the data in table 1, the liver blood flow in liters per minute can be calculated. Thus with a blood volume corresponding to 8.5 per cent of his body weight, a 75 Kg. man would have 6.4 liters of blood. Of this volume, 28.7 per cent or 1.8 liters will pass through the liver per minute. The average value for the blood volume obtained from measurements of labeled red blood cells summarized by Berlin and Lawrence[7] is 6.9 per cent of the body weight. This value may be preferable to the T-1824 value; when this value is used rather than the 8.5 per cent obtained from the T-1824 dye measurements in our study, the liver blood flow in the example cited becomes 1.5 liters per minute. This agrees almost exactly with liver blood flow values obtained by others using different methods.[1–4]

Table 2.—*Comparison of Arterial and Venous Sampling and of the Use of the Ratio* $\frac{Cr\ PO_4}{T\text{-}1824}$ *on the Value Obtained for the Disappearance-Rate Constant,* k

Subject	Arterial Curve k(min^{-1})	Venous Curve k(min^{-1})	Arterial Ratio Curve k(min^{-1})	Venous Ratio Curve k(min^{-1})
CHA	0.346	0.289	0.315	0.289
RIC	0.330	0.267	0.301	0.289
KIR	0.302	0.289	0.289	0.315
LIE	0.257	0.248	0.257	0.248
BID	0.289	0.267	0.267	0.267
	0.305 ± 0.015	0.272 ± 0.008	0.286 ± 0.014	0.282 ± 0.013

The disappearance rate constant, k, which represents the fraction of the blood volume perfusing the liver per minute appears to be a very satisfactory method for expressing the liver blood flow. It avoids the discrepancies which have been observed in the various methods of blood volume measurement. It has more physiologic significance than the simple quantitative flow expressed in liters per minute because it reflects the extent of equilibration between the liver and the other body tissues. As far as the metabolic interrelation between the liver and the other body tissues is concerned the colloid disappearance-rate constant may be of even greater significance than the blood-tissue perfusion factor.

A similar constant for the rate of removal of

bromsulfalein is discussed by Ingelfinger and co-workers.[8] They term their constant "percentage disappearance rate" (P.D.R.). Its average value is considerably smaller than the average value for k obtained with chromic phosphate because of the relative inefficiency of the liver for the removal of bromsulfalein as compared with chromic phosphate. The inefficiency of the extraction of bromsulfalein in a single passage precludes the use of this single injection method for the calculation of liver blood flow.

Repeated measurements of liver blood flow in the same individual employing chromic phosphate have been found to agree, indicating no difficulty with the saturation effects proposed by Inglefinger and co-workers in their studies with bromsulfalein.

A comparison of the values of k obtained from simultaneous arterial and venous data in five individuals is shown in table 2. The difference between the average k values obtained from arterial and venous curves is small, amounting to only 10 per cent. This difference becomes even smaller, less than 2 per cent, when the arterial and venous ratio curves are compared. This data implies that venous sampling is adequate for obtaining the disappearance constant, k, in normal individuals.

The ratio ($CrPO_4$/T-1824) curves as already shown in figure 2 present an initial horizontal portion. The duration of this lag probably represents the summation of the arm-to-arm circulation time and the time of splanchnic transit. The slope following the initial lag represents the rate of disappearance of colloid from the labeled blood pool, which is constantly expanding during the mixing period, and consequently might be expected to show a changing slope. The magnitude of this change should be a function of the relative magnitudes of the cardiac output and the circulating blood volume. The data obtained in this study do not uniformly show a changing slope possibly because in the normal individuals investigated, differences between the magnitude of cardiac output and circulating blood volume were not sufficiently great. Furthermore, any minor differences that may have existed would tend to be obscured by rapid mixing.

Summary

1. A method for calculating the liver blood flow by means of the rate of disappearance of colloidal chromic phosphate from the blood has been reviewed.

2. This method has been applied to the study of liver circulation in a group of 29 fasting normal men.

3. The significance of the colloid disappearance-rate constant as a physiologic expression of the liver blood flow has been discussed.

4. The average value obtained for k in the normal group studied was 0.287 ± 0.007 minute^{-1}. Depending upon the value accepted for the blood volume this will give a liver blood flow of from 1.5 to 1.8 liters per minute.

5. Extrahepatic colloid localization, hepatic efficiency for colloid removal, speed of mixing, and type and time of sampling have been discussed.

Sumario Español

Un método para calcular la circulación hepática por medio de la velocidad de desaparición de fósfato crómico coloidal de la sangre se describe. Este método se ha aplicado al estudio de la circulación hepática en un grupo de 29 sujetos normales en ayunas. El significado del constante de velocidad de desaparición del coloide como una expresión fisiológica de la circulación hepática se discute y el valor promedio obtenido para esta constante en sujetos jovenes normales fue 0.287 ± 0.007 min. $^{-1}$. Se discute la localización extrahepática del coloide, la eficiencia hepática para remover el coloide, la velocidad de mezcla y el tipo e intérvalo de la toma de muestras.

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Successful Prevention of Experimental Hypercholesteremia and Cholesterol Atherosclerosis in the Rabbit

By O. J. Pollak, M.D., Ph.D.

Cholesterol is absorbed by rabbits while its stereoisomer, sitosterol, is not resorbed. Cholesterol and sitosterol form nonseparable crystals. When the two sterols were fed simultaneously to rabbits, cholesterol was not absorbed, or was absorbed but partly. The degree of prevention of hypercholesteremia depended upon the amount of sitosterol fed with the cholesterol. A six-fold surplus of plant sterol was required in the experiments because the product employed contained but 75 to 80 per cent of sitosterol and because the supplied sitosterol binds not only exogenous cholesterol but also endogenous cholesterol present in the intestines. In the rabbit, prevention of hypercholesteremia is tantamount to prevention of atherosclerosis induced by cholesterol feeding.

RABBITS and other animal species fed cholesterol over a period of time develop hypercholesteremia which commonly leads to cholesterol atherosclerosis. Students of the steroid metabolism have long been impressed by reports on the inability of herbivorous and omnivorous animals to resorb phytosterol.

Von Gierke[1] claimed that rabbits absorb phytosterol in the same manner as cholesterol, and Nikuni[2] stated that mice can resorb phytosterol esters. Bondzynski and Humnitzki[3] and Dorré and Gardner[4] identified equine fecal sterols as those of hay. Fraser and Gardner[5] fed phytosterols to rabbits for from five to nine days: none were resorbed. Comparable series of rabbits, rats, mice, cats and a dog were fed by Schönheimer[6] sitosterol, cholesterol, or neither sterol, respectively. Sitosterol was not resorbed by a single animal of these species. The identity of excreted sterols with the dietary sterols was proved by analysis of the feces. Yuasa[7] found no increase in the cholesterol of portal vein blood of three dogs fed sitosterol. Schönheimer and coworkers[8] failed to recover plant sterols in thoracic duct fluid of dogs fed peanut oil sterols. Schoenheimer[9] also fed to dogs cholesterol and phytosterol simultaneously but found only cholesterol in thoracic duct fluid. Rosenheim and Webster[10] fed beta-sitosterol to 42 rats for a short time, without resorption. Altschul[11] fed two rabbits 0.3 Gm. stigmasterol daily for 73 and 116 days, and treated two other rabbits percutaneously with this sterol. Neither animal developed anatomic alterations. Thus, while various investigators employed different plant sterols and experimented with different animal species, 9 out of 11 investigators arrived at the conclusion that plant sterols are not resorbed.

The terms "phytosterol" and "plant sterol" are rather complex. The number of known plant sterols is large and the number of not yet known plant sterols probably larger. The selectivity of the intestinal wall with regard to resorption of sterols has been investigated by Schönheimer and his group.[12] Even slight changes in the structure of a sterol will make it nonresorbable. Some of the many phytosterols might be resorbable to a slight extent; some sterols of animal origin are but partially resorbable, according to Sperry and Bergman.[13]

Sitosterol, the stereoisomer of cholesterol, is one of the nonresorbable plant sterols. Sitosterol forms nonseparable crystals with cholesterol. The question was asked whether sitosterol fed simultaneously with cholesterol to rabbits would prevent resorption of cholesterol or whether cholesterol would, in such instance, make sitosterol resorbable.

From the Quincy City Hospital, Quincy, Mass., and the Kent General Hospital, Dover, Del.

Supported partly by a grant from the National Heart Institute.

Materials and Methods

Buck rabbits of fairly uniform breed, age and weight were used in this study. Their weight was between 2400 and 2760 Gm.; it averaged 2600 Gm.

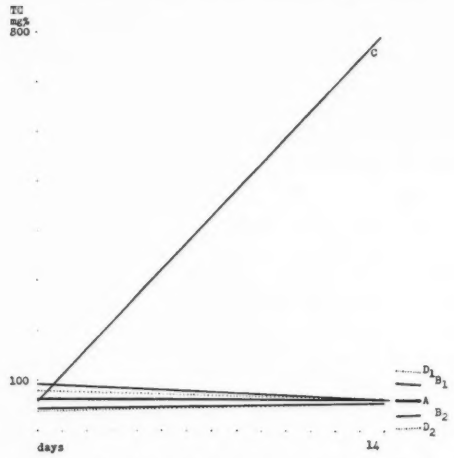

Fig. 1. Total blood cholesterol (TC) in milligrams per 100 ml. in control series "A–D."

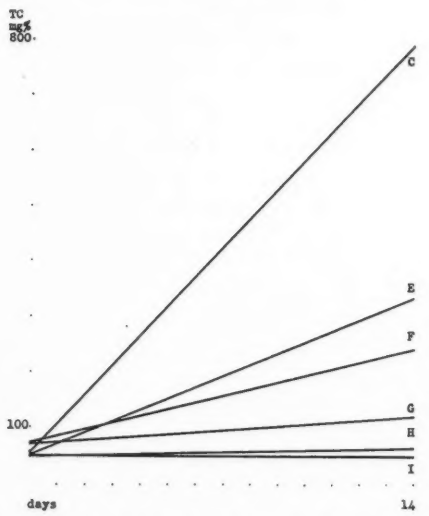

Fig. 2. Total blood cholesterol (TC) in milligrams per 100 ml. in the positive control series "C" and in experimental series "E–I."

The animals were fed Purina Rabbit Chow supplemented by a moderate amount of greens from the kitchen and by water. The experiments were conducted in fall, in winter and in spring of 1950–51 and 1951–1952.

Some groups of animals received cholesterol (c.p., Pfanstiehl) and some received "sitosterol," that is, mixed plant sterols from soy beans containing from 75 to 80 per cent sitosterols (Distillation Products Industries). Other groups of rabbits received both types of sterols in various proportions. Such sterols were suspended in a mixture of two parts of cottonseed oil and one part of 95 per cent ethyl alcohol. Twenty per cent suspensions of sterols were prepared in the oil-alcohol mixture in a Waring blendor. Rabbits were fed the suspension in a single dose, by stomach tube. The tube was injected from a syringe holding the thick liquid material. Control animals were fed the oil-alcohol mixture in a like manner.

Table 1.—*Outline of Experiment*

Group	No. of rabbits	Treatment (Gm./day)
A	10	Normal diet
B	10	Oil-alcohol mixture, 15 cc.
C 1	5	Cholesterol, 1 Gm.
C 2	5	Cholesterol, 1.5 Gm.
D 1	5	Sitosterol, 1 Gm.
D 2	5	Sitosterol, 2 Gm.
D 3	5	Sitosterol, 3 Gm.
D 4	5	Sitosterol, 5 Gm.
D 5	5	Sitosterol, 6 Gm.
D 6	5	Sitosterol, 7 Gm.
D 7	5	Sitosterol, 10 Gm.
E	10	Cholesterol, 1 Gm., sitosterol, 1 Gm.
F	10	Cholesterol, 1 Gm., sitosterol, 3 Gm.
G	10	Cholesterol, 1 Gm., sitosterol, 5 Gm.
H	10	Cholesterol, 1 Gm., sitosterol, 6 Gm.
I	10	Cholesterol, 1 Gm., sitosterol, 7 Gm.

Cholesterol determinations by the Schoenheimer-Sperry technic were made prior to the experiment, repeatedly during the study, and at the close of the observation period. Average values for total cholesterol were charted in the form of graphs (figs. 1 and 2). In the text, average values for total, free and ester cholesterol are reported.

All rabbits were autopsied a day after termination of observation. Multiple tissue blocks from large vessels and all the viscera were processed and sections stained by several methods.

The mixed soy sterols fed to rabbits are referred to as "sitosterol," in the text. In the outline of the study, groups C and D are subdivided (C 1, 2; D 1, 2, 3, 4, 5, 6, 7) according to the amount of sterol fed daily to each rabbit. In the report of results, subdivision is different: Groups B and D are

separated according to the initial blood cholesterol level (B 1, 2; D 1, 2).

Results

*Control Series**

Group A. Rabbits kept on our standard diet had stable cholesterols, regardless of the height of the levels. Minimum and maximum blood cholesterol levels expressed per 100 ml. were 40 and 92.5 mg. for total, 14 and 28.5 mg. for free, and 36 and 64 mg. for ester cholesterol. The free cholesterol was from 25.8 to 37 per cent of the total blood cholesterol. The average values for total, free and ester cholesterols in the control group were 62, 21, and 41 mg. per 100 ml. of blood, respectively; the average percentage of free cholesterol was 32 per cent of the total. Gross and microscopic postmortem examinations were entirely negative.

Group B. Rabbits in this group received daily 15 ml. of cottonseed oil–ethyl alcohol mixture. Four animals in this group had a high normal blood cholesterol (B_1) and six had a low normal level (B_2). Average initial cholesterols in group B_1 were 92, 28, and 64 mg. per 100 ml. of blood; final values were 60, 15, and 45 mg., for total, free and ester cholesterol. All four rabbits (B_1) developed diarrhea while none of the other six rabbits (B_2) reacted to the feeding. In group B_2, blood cholesterols averaged 46, 14, and 32 mg. per 100 ml., at the onset, and 56, 17, and 39 mg., at the close of the two week feeding period. Gross and microscopic tissue examination was negative in all animals of the series.

Group C. Five rabbits (C_1) received 1 Gm. and five others (C_2) were fed 1.5 Gm. cholesterol, daily. Differences in response to feeding were too slight to warrant subdivision of the group. Starting average blood cholesterol levels were 57, 21, and 36 mg. per cent, for total, free and ester cholesterol. After two weeks, the three corresponding values were 800, 211, and 589 mg. Of the 10 rabbits, 9 had a few grossly visible, yellowish patches in the ascending aorta. Microscopically, all nine rabbits had cholesterol atherosclerosis of the aorta and, in addition, three had subintimal foam-cell deposits in the carotid arteries.

* Summarized in figure 1.

Group D. Groups of five rabbits were fed respectively 1 Gm. (D_1), 2 Gm. (D_2), 3 Gm. (D_3), 5 Gm. (D_4), 6 Gm. (D_5), 7 Gm. (D_6), and 10 Gm. (D_7) of sitosterol. The difference in blood cholesterol levels after two weeks of feeding was moderate and unrelated to the amount of sterol ingested. Subdivision of results into seven fractions is unnecessary. In analogy to group B_1 and B_2 with high normal and low normal hemocholesterols, respectively, the whole group D is similarly subdivided into D_1 and D_2, with 19 animals in the first and 16 in the second category. Average values for total, free and ester cholesterol of group D_1 were 77, 20, and 57 mg. per 100 ml. of blood, at the onset, and 63, 21, and 42 mg. at the end of feeding. In group D_2, the initial values were 40, 14, and 26 mg., and the terminal ones were 56, 17, and 39 mg. per 100 ml. Neither deviation can be held significant. No anatomic gross or microscopic alterations were observed in any rabbit of group D.

*Experimental Series**

Group E. Rabbits in this group received daily a mixture of 1 Gm. of cholesterol and 1 Gm. of sitosterol. Average initial and terminal total, free and ester cholesterols were 51, 18, and 33 mg. and 337, 111, and 226 mg. per 100 ml., respectively. None of the 10 rabbits had gross anatomic alterations. In two rabbits, isolated foam cells were seen in sections from the ascending aorta. The foam cells were round, were seated in the uppermost intimal layer, and mostly protruded into the vascular lumen. The nuclei of these cells were small and often pushed toward the cell membrane by the foamy protoplasm.

Group F. This group of rabbits received daily 1 Gm. of cholesterol and 3 Gm. of sitosterol. Total, free and ester cholesterols averaged 71, 22, and 49 mg. at the start and 246, 76, and 170 mg. per 100 ml. of blood at the close of the feeding period. Neither gross nor microscopic lesions were found in these rabbits.

Group G. This group of animals was fed 1 Gm. of cholesterol and 5 Gm. of sitosterol,

* Summarized in figure 2.

daily, for two weeks. Before the feeding, hemocholesterols averaged 65, 16, and 49 mg., and after feeding, they were 123, 43, and 80 mg. per 100 ml., for total, free and ester cholesterol. Anatomic studies were negative in the group.

Group H. These rabbits were fed 1 Gm. of cholesterol and 6 Gm. of sitosterol per day. Starting cholesterols averaged 49, 13, and 36 mg. and final average values were 62, 17, and 45 mg. per 100 ml. of blood. Anatomic studies were entirely negative.

Group I. In this group, rabbits received 1 Gm. of cholesterol and 7 Gm. of sitosterol daily. Initial and terminal averages for total, free and ester cholesterols were the same, that is 50, 16, and 37 mg. per cent. Anatomic findings were negative.

Discussion

Blood chemical assays in normal rabbits (group A, and initial levels in all other groups) illustrated the wide normal range of cholesterol values and also the variations in the proportion of free to total cholesterol. About one-half of rabbits fed cottonseed oil (group B_1) developed diarrhea. Rapid evacuation of intestines lead to lowering of blood cholesterols. None of the animals fed cholesterol, sitosterol, or both sterols developed diarrhea. All rabbits fed cholesterol (group C) rapidly developed hypercholesteremia. Free blood cholesterol increased, on the average, 10 times, and ester cholesterol increased sixteenfold, within two weeks. Successful production of cholesterol atherosclerosis confirmed this group (C) as positive control while failure to induce vascular changes through sitosterol feeding established that group (D) as negative control. Sitosterol feeding failed to influence the blood cholesterols of rabbits (group D), regardless of the dose fed. It may be concluded that rabbits do not resorb sitosterol.

The results of combined cholesterol-sitosterol feeding to rabbits (groups E–I) are best evaluated in comparison with positive (C) and negative (D) controls as shown in table 2.

The question whether phytosterol added to various diets can influence blood and organ cholesterols was asked by Schettler.[14a] He fed 10 mice daily a diet of skimmed milk and oats with 500 mg. sesame oil or dog's depot fat and with 20 mg. soy sterol added. Blood cholesterol was assayed before feeding and on the fifth, seventh, fourteenth, twenty-first and forty-second days during the feeding. Liver, spleen and kidneys were analyzed after death. In no instance was cholesterol affected. There are two reasons for failure of Schettler's experiments: According to the investigator,[14b] first, the composition of the soy sterols was not known except for their 25 per cent stigmasterol content, and second, but 20 mg. phytosterol was used against 500 mg. cholesterol.

Table 2

Group	C (Gm.)	S (Gm.)	TC Increase	Alterations
C	1	0	14 ×	9 ×
D 1	0	1	0	0
D 3	0	3	0	0
D 4	0	5	0	0
D 5	0	6	0	0
D 6	0	7	0	0
E	1	1	6 ×	2 ×
F	1	3	3 ×	0
G	1	5	2 ×	0
H	1	6	¼ ×	0
I	1	7	0	0

TC, total cholesterol; C, cholesterol; S, sitosterol.

Peterson[15] experimented with chickens about the same time the experiments with rabbits which we are reporting were under way. He used the same soy sterols in cottonseed oil employed for feeding rabbits. He observed similar inhibition of induced hypercholesteremia as was seen in rabbits. In chickens, sitosterol was effective if fed in thrice the amount of cholesterol (3:1). In rabbits, sixfold excess of sitosterol over cholesterol (6:1) was needed to obtain the same results.

Theoretically, one molecule of sitosterol should bind one molecule of cholesterol. The need for surplus sitosterol can be explained to some extent. According to Sperry,[16] a portion of endogenous cholesterol is excreted into the digestive tract. Some of this cholesterol

is reabsorbed. Part of the excess sitosterol might be needed to neutralize endogenous cholesterol present in the intestines. Gould and Taylor[17] demonstrated that in rabbits cholesterol synthesis fluctuates in reverse ratio to the dietary supply of cholesterol. Addition of sitosterol to the diet prevents resorption of cholesterol and thus might stimulate endogenous cholesterol production. In turn, additional sitosterol would be required to bind cholesterol. Certainly, the relationships are not that simple for if they were, reduction of blood cholesterol would only be possible through depression of cholesterol synthesis. Another reason for the need of surplus sitosterol in experiments with rabbits fed cholesterol lies in the fact that the plant sterols used contained but 75 to 80 per cent of sitosterol, while chemically pure cholesterol was used. Lastly, the proportion between alpha-, beta- and gamma-sitosterol in the material used is not known, and it is quite possible that but one or two of these three sitosterols have the desired effect.

It is known that a mixture of *d*- and *l*-epinephrine is physiologically inactive. A mixture of the stereoisomers cholesterol and sitosterol is nonresorbable. From solutions in ethanol or equal parts of acetone and 95 per cent ethyl alcohol containing cholesterol and also sitosterol, a single type of crystal is obtained. The two components cannot be separated by recrystallization or by partition chromatography. This physical phenomenon might explain the inhibition of cholesterol resorption by the nonresorbable sitosterol.

Summary

1. The bibliography on administration of plant sterols to animals has been summarized.

2. The view that rabbits do not absorb sitosterol has been confirmed, experimentally.

3. Simultaneous feeding of cholesterol and sitosterol results in mitigation or in complete inhibition of hypercholesteremia commonly resulting from feeding cholesterol to rabbits. The effect depends upon the ratio of the two sterols used.

4. By feeding a sufficient amount of sitosterol with the cholesterol the production of cholesterol atherosclerosis, commonly induced by feeding cholesterol to rabbits can be prevented.

5. The need for excess sitosterol in the experiments described is discussed.

6. The mechanism of interaction of cholesterol and sitosterol is considered.

Acknowledgments

The valuable aid of Zacharias Komninos, M.D., and Mrs. Bella Wadler, M.S., is gratefully acknowledged.

Sumario Español

El colesterol se absorbe en los conejos mientras que su estereoisomero no se absorbe, colesterol y sitosterol forman cristales no separables. Cuando los dos esteroles fueron ingeridos simultáneamente por conejos, colesterol no se absorbió, o se absorbió pero solo parcialmente. El grado de prevención de la hipercolesteremia dependió de la cantidad de sitosterol proporcionada con el colesterol. Una cantidad 6 veces mayor de esterol de plantas se necesitó en estos experimentos debido a que el producto empleado contenía solamente de 75 a 80 por ciento de sitosterol y debido a que el sitosterol proporcionado liga no tan solo el colesterol exógeno pero si también el colesterol endógeno presente en los intestinos. En el conejo, la prevención de hipercolesteremia es equivalente a la prevención de la ateroesclerosis inducida por alimentación de colesterol.

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Reduction of Blood Cholesterol in Man

By O. J. Pollak, M.D., Ph.D.

Dietary cholesterol contributes to the development and maintenance of hypercholesteremia in man. Intake of sitosterol prevents cholesterol resorption. This results in lowering of blood cholesterols to a basal endogenous level. Upon cessation of sitosterol intake hemocholesterols return to the original level. Excess supply of plant sterol was required in clinical experiments because the material used contained but 75 to 80 per cent of sitosterol and because of the large amount of endogenous cholesterol which has to be inactivated by the sitosterol, besides exogenous cholesterol.

SEVERAL human diseases are accompanied by hypercholesteremia. For some diseases, elevation of blood cholesterol is diagnostic. A majority of physicians believe that in patients with acquired hypercholesteremia, as in persons with idiopathic familial hypercholesteremia, atherogenesis and atherosclerosis is more frequent than in persons with normal hemocholesterol levels.

For the purpose of this paper the question whether cholesterol is the primary damaging agent or is deposited in previously altered arteries is less important than is the fact that cholesterol is regularly found in human atherosclerotic lesions and that many manifestations of the disease are caused by the presence of cholesterol in the vessel wall. These facts seem to make reduction of blood cholesterol in man desirable.

Notwithstanding sporadic reports on the efficacy of various drugs, the only effective means of reducing blood cholesterol in man is the complete restriction of cholesterol and fat intake.

Mellinkoff, Machella and Reinhold[1] observed that in 13 out of 14 patients who were kept on protolysate-dextrimaltose the blood cholesterol level dropped. They plotted two representative curves; in both patients, free and ester cholesterol decreased at the same rate and returned promptly to the original height on cessation of treatment. Keys, Mickelsen, Miller and Chapman[2] placed series of men on diets restricted partially or completely in cholesterol. A strict rice-fruit diet, void of cholesterol, resulted in a drop of blood cholesterol. Groen, Tjiong, Kamminga and Willerbrands[3] conducted well controlled studies with 60 persons on alternating low and high cholesterol diets. They observed in most persons oscillation of blood cholesterol with the amount of cholesterol in food. Many other factors influenced hemocholesterol levels. Hildreth, Mellinkoff, Blair and Hildreth[4] succeeded in reducing blood cholesterol by dietary restriction of fat without particular restriction of dietary cholesterol. They interpreted their findings as being the result of diminished production of endogenous cholesterol due to a reduced supply of acetates.

The results of experiments with rabbits reported in a preceding paper[5] warranted a trial of sitosterol as anticholesteremic agent. The statement that plant sterols are not resorbed by human beings can be found in many texts. The complete bibliography based on evidence and not on hear-say is here reproduced in translation from the German language: "One person was given [by Schönheimer*] for two days 1 Gm. (total, 2 Gm.) of peanut oil sterols in butter. No resorption occurred as the unsaturated sterols could be recovered in feces."[6] The paper from which the cited sentences are taken contains on the same page a third pertinent sentence which reads: "Many years ago, the same experiment was performed [by Windaus†] with the same results."[7]

Materials and Methods

Investigation of various sources‡ led to a plant sterol mixture (Distillation Products Industries)

From the Quincy City Hospital, Quincy, Mass., and the Kent General Hospital, Dover, Del.

* Inserted by author.

† Inserted by author.

‡ In the fall of 1950.

which contained 75 to 80 per cent of sitosterols. For practical purposes, we refer to this material as "sitosterol." The product has a low specific gravity, is light, bulky and lumpy. It has a chalky appearance and taste, a dirty, off-white color, and a gritty, sticky consistency. Many attempts were made to convert it into a palatable product and experiments are still under way. In the original form in which it was used during this study the material was unpleasant to take. Most volunteers ate it for but short periods—for from two to four weeks—especially as the experiment involved, besides the ingestion of sitosterol, multiple blood lettings and other procedures.

tory. In groups of from three to four persons on sitosterol regimen, the following were checked: basal metabolism rate, water balance, electrolyte balance, blood lipid fractions, protein fractions, blood sugar, urinary 17-ketosteroids and progesterone. All clinical and chemical determinations were made repeatedly before, during, and after the experimental period.

In all probants, total, free and ester cholesterol were determined in duplicate, periodically. Blood was taken every fifth day or every seventh day during the period of sitosterol intake, and for some time thereafter. The Sperry-Schoenheimer[8] method was used, and, toward the close of the study, also the method of Pollak and Wadler.[9]

TABLE 1.—*Initial and Minimum Total Blood Cholesterol Levels (in mg. per 100 ml.) in Twenty-Six Healthy Persons on Sitosterol Regimen*

No.	Initial TC mg. %	Daily Dose S Gm.	No. of days	Minimum TC mg. %	No.	Initial TC mg. %	Daily Dose S Gm.	No. of days	Minimum TC mg. %
1	414	10	14	264	14	270	10	7	190
2	402	10	14	242	15	268	5	7	192
3	364	7	7	246	16	266	5	15	202
4	337	7	7	201	17	254	10	15	210
5	333	10	14	226	18	250	5	7	192
6	324	10	14	222	19	240	7	14	207
7	290	7	10	163	20	230	10	21	152
8	288	10	14	147	21	200	7	28	184
9	287	7	15	136	22	198	5	20	178
10	274	7	15	226*	23	186	7	7	147
11	273	10	7	231	24	173	7	28	166
12	271	10	15	202	25	144	10	7	142
13	270	10	7	215	26	126	7	21	132

TC, total blood cholesterol.

S, sitosterol.

* This case charted; in this person, as in others, on a second course of sitosterol a lower minimum was obtained.

On and off, 26 persons took varying amounts of the sitosterol for varying periods of time. The daily intake was 5 Gm. divided into two doses, or 7 Gm. or 10 Gm. divided into three roughly equal doses taken with meals. The shortest period was eight days and the longest single feeding period was eight months. Some persons took sitosterol intermittently, for as long as 14 months. All persons were on their usual diet. No restriction of alimentary cholesterol and fats was attempted. Such modifications were left for future studies. Some probants occasionally indulged in fat- and cholesterol-rich meals, as evidenced by strongly lipemic blood serum the following morning.

Our experiments were designed to verify that sitosterol is not resorbed by man and that its intake is harmless and does not interfere with the metabolism of foodstuffs other than cholesterol. Careful histories of dietary and other habits were taken, on each visit. Attention was paid to body weight, bowel movements, blood pressure, and to menstrual his-

RESULTS

The outcome of clinical and laboratory studies was satisfactory. The following were deviations from the norm: One man had gall bladder colic with discharge of a calculus after he had taken 7 Gm. of sitosterol daily for eight days. The episode was held to be coincidental. One probant developed a chalazion after he had been on 10 Gm. of sitosterol per day for over four weeks. Another chalazion developed in this man five weeks after termination of the sitosterol regimen. In a single middle-aged man who had taken the material for over one year, with but short interruptions, the blood pressure dropped rather suddenly from 152/110 to 162/92. Six months after cessation of sitosterol intake, the blood pressure

was still low. The excretion of steroid hormones oscillated within normal limits. All clinical and laboratory data remained unchanged throughout the study save for blood cholesterol values.

The effect of dietary intake of sitosterol on hemocholesterol levels was sufficiently significant to warrant a preliminary report. Because of the many variants in the experiments, summation of results proved difficult. Therefore, only the initial and minimum values for total blood cholesterol were tabulated, together with the daily dose of sitosterol and the period for which it was taken. (See table 1.) A single

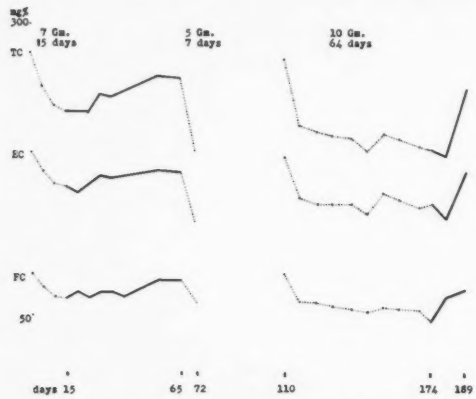

FIG. 1. Total, ester and free blood cholesterol (in milligrams per 100 ml.) in a healthy person taking sitosterol for three periods.

TC, total blood cholesterol; EC, ester cholesterol; FC, free cholesterol; dotted line, cholesterol levels during sitosterol regimen; solid line, cholesterol levels during sitosterol-free intervals.

experiment is reported in the form of graphs for total, ester and free cholesterol. (See fig. 1.)

The data in table 1 and figure 1 illustrate that there are individual variations in the response to sitosterol intake. In some persons, the daily dose and the total dose of sitosterol required to lower the blood cholesterol level may be twice the dose required in other persons with comparable initial levels. The response of free and ester cholesterol was almost always the same and the percentage of free to total cholesterol varied but slightly for each probant. No differences were seen in persons of different age, or between the response of men and women. Upon daily doses of 5, 7, or 10 Gm. of sitosterol, the minimum blood cholesterol level was reached within 7 to 14 days. Further decreases after this period were but slight, even when 10 Gm. were taken for two months. The higher the original blood cholesterol level the easier it was to depress it. Blood cholesterol levels below 200 mg. per 100 ml. could not be influenced. The more rapid and the more complete the depressions of total, free and ester cholesterol levels were, the more rapid was the return of these levels to the original height after the administration of sitosterol was stopped. In some individuals the return required 14 days and in others as long as 40 days.

Attention should be directed to the sudden elevation of values in the three curves shown in figure 1 during the third period of sitosterol intake. Such temporary increases in the blood cholesterol values were noted in four persons, at one time or another. In each case, a history of diarrhea lasting two to three days prior to cholesterol rise was obtained. Evacuation of the bowel and the resulting removal of sitosterol apparently had the same effect as interruption of sitosterol intake.

DISCUSSION

Medical literature contains multiple references to relatively low blood cholesterol values in populations habitually on a low fat and low cholesterol diet and in people of war torn countries whose dietary supply of fats was restricted. It is not quite clear whether in these people a low hemocholesterol is the result of low cholesterol intake, of low fat intake, of restriction of both, of a low supply of fatty acids which normally further cholesterol resorption, of a reduced caloric intake, or of unknown factors. Possibly, a relatively high intake of proteins leads to relative hyperalbuminemia and stabilization of plasma colloids, including cholesterol and lipoproteins. The phenomenon could be due to an intake of sitosterol sufficient to prevent resorption of dietary cholesterol. Much attention is being paid to the foodstuffs missing from the diet of these persons, but little attention is paid to the relative or absolute increase of other nutrients. According to Lange,[10] who collected

all pertinent references, the largest amount of phytosterol (presumably, sitosterol)* is in oil of wheat germ, in oil of the common bean, in oil of rye germ and corn germ, in corn gluten and in the dry hull of hempseed, and in the leaves of kale and broccoli. It would be interesting to learn the sitosterol content of diets in people with low blood cholesterol values.

There is a striking similarity between the representative curves shown in this paper and those depicted by Mellinkoff and co-workers,[1] who maintained patients on protein hydrolysate. Deprivation of dietary cholesterol and prevention of resorption of cholesterol have the same effect: The fall of hemocholesterols is fairly rapid, at first, and then the curve gradually tapers off to a rather stable "basal" level. Further decrease of blood cholesterols cannot be accomplished by either method and might not be desirable. "Cholesterol tolerance tests" should start from the basal level, in analogy to glucose tolerance tests.

It may be assumed that the basal level is maintained through cholesterol synthesis. The amount of endogenous cholesterol in man is not yet well known. Likely, the production of endogenous cholesterol in man fluctuates, as in animals, inversely with the supply of exogenous cholesterol. Using the data of Lange[10] and of Okey,[11] the average intake of cholesterol in man can be estimated as from 300 to 900 mg. per day, averaging 580 mg. daily. London and Rittenberg[12] estimated the daily synthesis of cholesterol in man as equal to 546 mg. If calculations of Gould and Taylor[13] for dogs were valid for man, hepatic endogenous cholesterol synthesis would be 1.2 Gm. a day, that is about twice the ingested amount.

As in the rabbit,[5] excess sitosterol was required to prevent cholesterol resorption. Again, it must be pointed out that sitosterol has to bind exogenous and endogenous cholesterol, that the plant sterols used contained but 75 to 80 per cent of sitosterol, and lastly, that the proportions of alpha-, beta- and gamma-sitosterol in the product was not known. In man, one deals with many more factors than in the rabbit. The human diet varies from day to day and from meal to meal in quantity and quality. The physical and emotional life of man differs from the captive life of caged rabbits.

A complete cholesterol- and fat-free diet is, at best, a temporary measure. In the study with sitosterol, reduction of blood cholesterols was achieved in persons on unrestricted cholesterol and fat consumption. Certainly, study of persons on a partially reduced cholesterol-fat diet seems desirable. In such persons it should be possible to reduce the amount of sitosterol needed to reduce blood cholesterols.

Prevention of resorption of dietary cholesterol has been repeatedly attempted in animals. In man, a single trial has been made by Dam.[14] A person was given 3.45 Gm. of dihydrocholesterol divided over 12 meals. All of this sterol could be recovered in feces and the resorption of cholesterol was inhibited. The explanation for this occurrence is the same as for interaction of sitosterol and cholesterol, namely the formation of inseparable mixed crystals which are nonresorbable.

The approach discussed in this paper is not the only way in which the blood level of cholesterol can be reduced in man. The administration of sitosterol does appear to be a simple way to lower the blood cholesterol level.

This preliminary report should open a new avenue of research. Some day, the question as to the value of prophylactic or therapeutic reduction of blood cholesterol will be answered.

Summary

1. Sitosterol is not resorbed by man.

2. Oral intake of sitosterol does not interfere with health or with the metabolism of any foodstuff other than cholesterol.

3. Ingestion of sitosterol in proper amounts prevents intestinal resorption of cholesterol. This results in the lowering of blood cholesterols to the basal endogenous level.

4. Continuous administration of sitosterol is required for the maintenance of the basal blood cholesterol level.

Acknowledgment

The valuable aid of Mrs. Bella Wadler, M.S., is gratefully acknowledged.

* Inserted by author.

Sumario Español

El colesterol en la dieta contribuye al desarrollo y conservación de hipercolesteremia en el hombre. La ingestión de sitosterol evita la resorción de colesterol. Esto resulta en un decremento del colesterol sanguíneo a un nivel endógeno basal. Con la cesación de ingestión de sitosterol los esteroles sanguíneos retornan a su nivel original. Un exceso de suministro de esterol de planta se necesitó en estos experimentos clínicos por que el material usado contenía solamente de 75 a 80 por ciento de sitosterol y debido a la gran cantidad de colesterol endógeno que tiene que ser inactivado por el sitosterol además del colesterol exógeno.

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Electrophoretic and Ultracentrifugal Analysis of Serum Lipoproteins of Normal, Nephrotic and Hypertensive Persons

By LENA A. LEWIS, PH.D., AND IRVINE H. PAGE, M.D.

Using a method of ultracentrifugation which brings out clearly the α and β lipoprotein components of serum, studies of normal, hypertensive and nephrotic human beings have been made. There are striking differences in distribution of lipoproteins among the different ages and sexes. During the stages of active atherogenesis in hypertensives and nephrotics, both the α_2 and β lipoproteins and the lighter, higher molecular weight aggregates contribute importantly to the superabundance of plasma lipoproteins. The attribution of an exclusive atherogenesis to any one plasma fraction does not seem to us justified by these or other studies.

MACHEBOEUF[1] reported in 1929 the preparation from horse serum of a lipoprotein that had a constant lipid-protein composition. The first lipoprotein prepared by ultracentrifugation was by Pedersen[2] from human serum after addition of magnesium sulfate to 0.45 saturation. It had the sedimentation constant of β_1 globulin. Attempts to isolate lipoproteins from serum other than human were at that time unsuccessful. In 1949 Lewis and Page[3] obtained a lipoprotein from dog serum by ultracentrifugation after addition of sodium chloride to 1.5 M concentration. It had the electrophoretic mobility of α_2 globulin. Gofman and coworkers[4] studied lipoprotein concentrates obtained by flotation in the ultracentrifuge of protein solutions made to a density 1.063 by addition of sodium chloride, thus offering a new approach to the characterization of lipoproteins of serum. The number of lipoproteins definable and, correspondingly, the usefulness of this method of analysis was increased by raising the density to 1.21 by addition of potassium bromide as in the modification of Green, Lewis and Page.[5]

Electrophoretic analysis of plasma or serum proteins of patients with hypothyroidism, diabetes with retinitis, nephrosis, Cushing's syndrome or malignant hypertension has revealed many abnormalities. But one change common to all was a consistently increased concentration of β globulin.[6] In many, an elevated serum cholesterol was also present. These observations suggested to us that the increase in β globulin was likely due to increase in the lipoprotein fraction and that this increase was in some way associated with vascular disease.

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I. CENTRIFUGAL ANALYSIS

Methods

A concentrate of lipoproteins was prepared by centrifuging for 13 hours at 30,000 revolutions per minute (centrifugal force 63,000 × g) 5 ml. of serum to which sodium chloride and potassium bromide had been added to bring the density to 1.21. The top 1 ml., which had an oily or milky appearance, was removed and studied in the analytic ultracentrifuge at a density of 1.21 by the method of Gofman[4] using a speed of 52,640 revolutions per minute, equivalent to 250,000 × g. The designation of the unit of measurement, $-S_{1.21}$, represents a negative sedimentation or flotation rate of 1×10^{-13} cm. per second per dyne per gram at a density of 1.21 and a temperature of 26 C. For convenience, 1.21 will be omitted, but is to be understood when "−S" is employed in this paper.

Results

At a density of 1.21 at least three components, based on differences in flotation rate, are resolved in human serum −S(25–40), i.e., β_1 lipoprotein, −S(20–25), i.e., α_2 lipoprotein

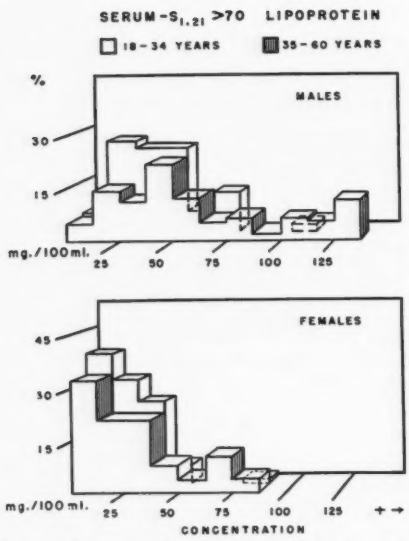

FIG. 1. Concentration of $-S > 70$ class of lipoproteins determined by ultracentrifugation of human serum of normal males and females respectively, 18 to 34 and 35 to 60 years of age.

and $-S(1–10)$, i.e., α_1 lipoprotein. In some sera $-S > 70$ and $-S(40–70)$ are also present. The point of maximum deflection which is used in designating the complexes is normally $-S$ 30 for the $-S(25–40)$ component, $-S$ 23 for $-S(20–25)$ and $-S$ 4 for $-S(1–10)$. If negative sedimentation rates deviate significantly from these figures, the observed values are given.

1. Normal Values. The $-S > 70$ concentration of 92 per cent of normal women between 18 and 60 years was less than 50 mg. per 100 ml. (67 persons, 42 being 18 to 34 and 25 being 35 to 60 years of age). The concentration was less than 75 mg. in 98 per cent of normal men between the ages of 18 and 34 (58 persons), and was greater in 27 per cent in the age group 34 to 60 (99 persons). (See fig. 1.)

The $-S(25–40)$ (the β_1 lipoprotein) was less than 150 mg. in 42 per cent of normal women between 18 and 34 years, contrasting with only 18 per cent of the older 34 to 60 year group. The $-S(25–40)$ was between 150 and

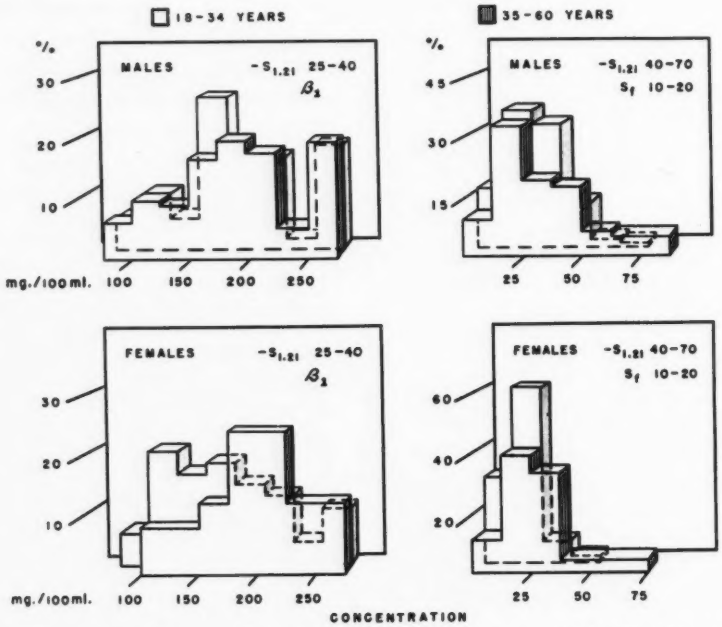

FIG. 2. β lipoproteins of serum of normal males and females respectively 18 to 34 and 35 to 60 years of age.

225 mg. in 62 per cent of the latter. In males the number in the younger group (11 to 34 years of age) having high β_1 lipoprotein was much increased, 72 per cent between 150 and 225 mg. In the group 34 to 60 years of age, males (58 per cent) and females (62 per cent) were alike. Taking the whole group, 20 per cent of males had β_1 lipoproteins greater than 250 mg., and only 9 per cent of females.

nificantly greater in the older women, i.e., 30 per cent with more than 250 mg. per 100 ml. of serum, than in the younger women, i.e., 10 per cent. In contrast, the α_1 fraction did not change as the men got older. Tables 1 and 2 summarize the normal human serum lipoprotein values.

2. Values in Subjects with Arterial Hypertension. The concentration of serum α and

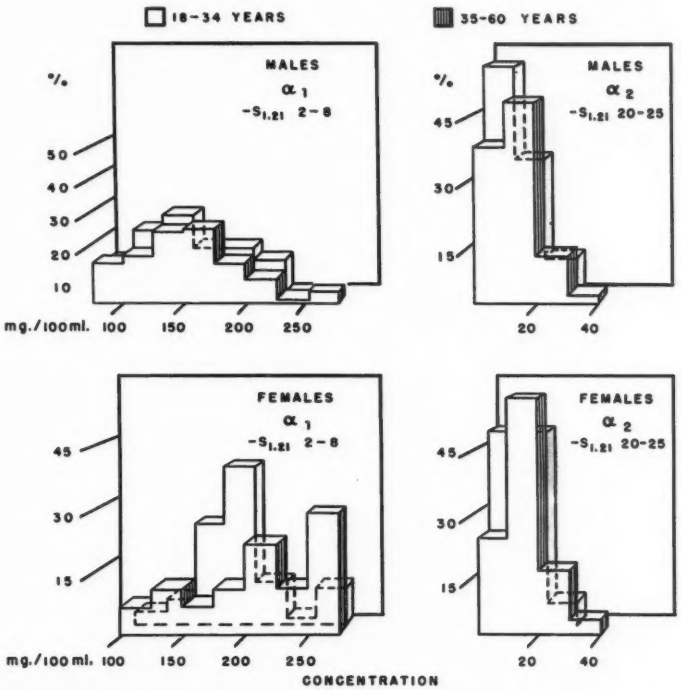

FIG. 3. α lipoproteins of serum of normal males and females respectively 18 to 34 and 35 to 60 years of age.

The $-S(40–70)$ (Gofman's S_f 10–20 fraction) concentration in both the younger and older age groups of the women was less than 38 mg. Eighty-seven per cent of the younger men and 72 per cent of the older were similarly less than 38 mg. per 100 ml. (fig. 2).

Most normal people have less than 20 mg. of α_2 lipoprotein (fig. 3), i.e., $-S(20–25)$, regardless of age or sex. The α_1 or $-S(2–8)$ fraction was more concentrated in women (12 per cent had less than 150 mg.) than in men (48 per cent had less than 150 mg.) It was also significantly greater in the older women, i.e., 30 per cent with more than 250 mg. per 100 ml. of serum, than in the younger women, i.e., 10 per cent. In contrast, the α_1 fraction did not change as the men got older. Tables 1 and 2 summarize the normal human serum lipoprotein values.

2. Values in Subjects with Arterial Hypertension. The concentration of serum α and β lipoproteins of 27 patients with mild essential hypertension was normal. The pattern in severe essential or malignant hypertension (88 cases) showed increased concentrations of $-S(40–70)$ and $-S(25–40)$ (β_1 lipoprotein). (See fig. 4.) There was moderate increase in concentration of α_2 lipoprotein, while β lipoprotein in the women showed a small decrease (fig. 5). The patients with the most severe renal disease exhibited greater increase in $-S(40–70)$ and the > 70 components, and the

TABLE 1.—*Average Normal Human Serum Lipoprotein Determined by Ultracentrifugal Analysis at Density 1.2*

Age	Males					Females				
	No. of Subjects	−S > 70	40–70	23	4	No. of Subjects	−S > 70	40–70	23	4
		mg./100 ml.					*mg./100 ml.*			
18–34	58	36.7 ± 3.8*	24.2 ± 1.8	11.6 ± 1.1	153.7 ± 5.1	42	21.8 ± 4.3	18.1 ± 1.4	11.6 ± 1.2	183.0 ± 8.4
35–60	99	59.5 ± 5.0	32.7 ± 1.8	12.4 ± 0.8	155.8 ± 4.8	25	22.0 ± 5.0	29.1 ± 4.2	13.3 ± 1.4	228.1 ± 11.6

* Standard error of the mean.

TABLE 2.—*Summary of Differences in Human Lipoprotein Levels, Grouped According to Age and Sex*

	−S > 70	40–70	23	4
F vs M				
18–34 yr. 18–34 yr.	+	+	0	+
F vs M				
35–60 yr. 35–60 yr.	+	0	0	+
F vs F				
18–34 yr. 35–60 yr.	0	+	0	+
M vs M				
18–34 yr. 35–60 yr.	+	+	0	0

+ = difference significant at 1% probability level
0 = difference not significant at 1% probability evel

peak of the β_1 fraction moved at a somewhat slower rate than normal.

During treatment of malignant hypertensive patients with pyrogens, very marked changes in the distribution of the lipoproteins were observed. There was a large increase in concentration of the −S > 70, −S(40–70) and β_1 lipoprotein. The α_2 lipoprotein concentration did not change significantly while the α_1 lipoprotein decreases greatly. On stopping treatment, or when the febrile response decreased due to development of tolerance, all lipoproteins tended to revert to pretreatment levels (fig. 6).

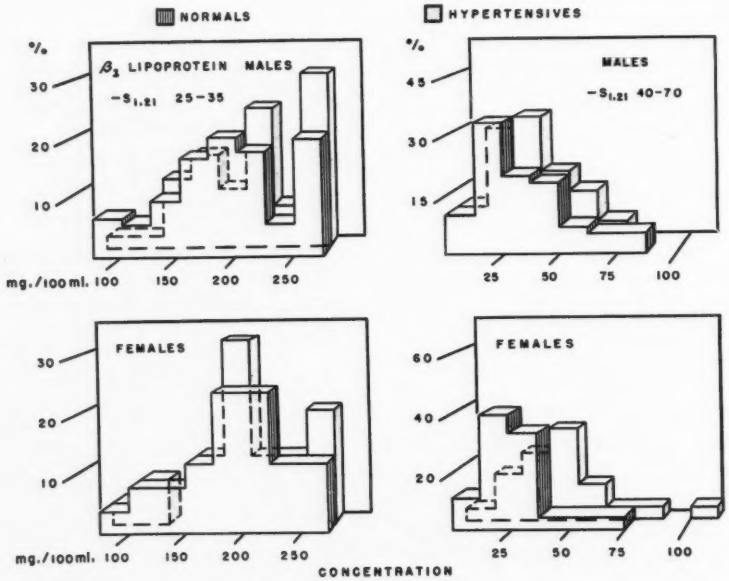

FIG. 4. β lipoproteins of serum of patients with severe essential or malignant hypertension, compared with those of normals of the same age (35 to 60 years of age).

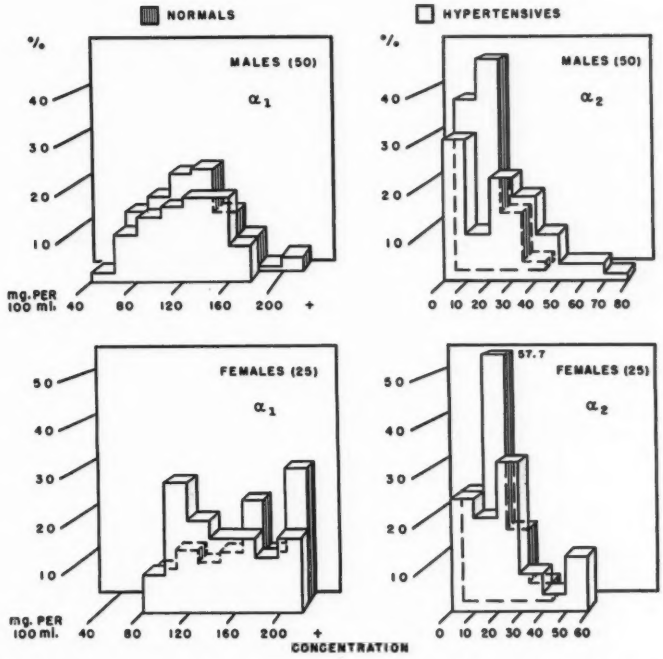

FIG. 5. α lipoproteins of serum of patients with severe essential or malignant hypertension compared with those of normals of the same age (35 to 60 years of age).

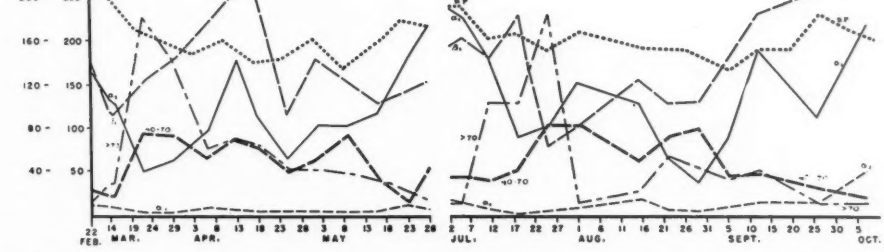

FIG. 6. Serum lipoprotein patterns of patient with malignant hypertension during treatment with pyrogen. Lipoproteins determined by ultracentrifugation at density 1.21.
. . . . . blood pressure; — — — — — β lipoprotein; ———— α_1 lipoprotein; — — — — — $-S(40-70)$; — — — — — $-S > 70$; - - - - - - - - - α_2 lipoprotein.

The lipoprotein pattern of malignant hypertensives receiving other types of therapy, that is, 1-hydrazinophthalazine, hexamethonium, low sodium diet or sodium nitroprusside, showed no changes comparable to those that occurred during pyrogen treatment. The patterns obtained on one patient, while receiving 1-hydrazinophthalazine or hexamethonium and hydrazinophthalazine, are shown in figure 7. Variations in the concentration of the com-

ponents seemed to be independent of each other and to have little relation to either the type of treatment or to arterial pressure.

3. Values in Patients with the Nephrotic Syndrome. The serum lipoprotein pattern of patients in the nephrotic phase of nephritis was bizarre. The concentration of the rapidly rising components $-S > 70$, and $-S(40–70)$ was increased, and $-S$ 30 (β_1) and $-S$ 23 (α_2) which normally are well resolved, separated poorly and were much increased in concentration (table 3). The first analysis on patient 7 was taken March 15, 1951, during the stage of acute nephritis. Before treatment was started the $-S > 70$ was elevated to 130 mg., the $-S(40–70)$ to 90 mg. and the β_1 and α_2 lipoprotein components showed no separation. The wide spread of the peak indicated its heterogenous nature. The two, β_1 and α_2, were present in a concentration of over 260 mg. per 100 ml. The α_1 lipoprotein was within normal limits throughout the study. The electrophoretic pattern was typical of that observed in the nephrotic syndrome, albumin 0.92, γ globulin 0.37 Gm. per 100 ml. with very large α_2 and β globulin components. Following a course of nitrogen mustard, 0.1 mg. per kilogram intravenously daily for four days, progressive clinical improvement, especially in renal function, was observed. The lipoprotein pattern and electrophoretic pattern reverted toward normal finally becoming so three months after the nitrogen mustard was initiated. The serum cholesterol concentration had decreased from an initial value of 1380 mg. to 257 mg. per 100 ml.

In contrast with patient 7, patient 9 showed no clinical improvement during the period of study, and the serum lipoprotein and electrophoretic patterns remained abnormal.

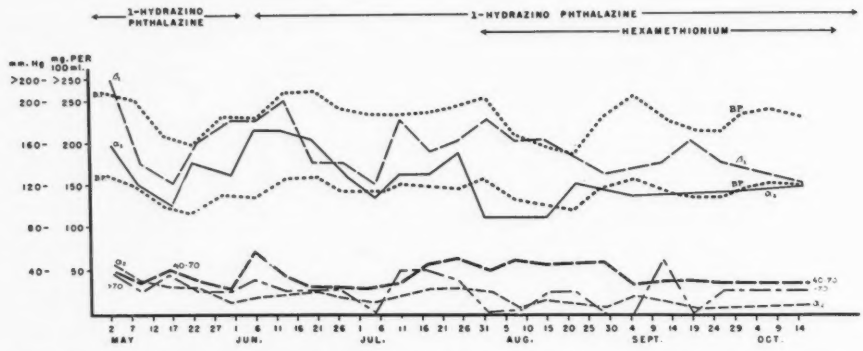

FIG. 7. Serum lipoprotein patterns of patient with malignant hypertension during treatment with 1-hydrazinophthalazine or hexamethonium and hydrazinophthalazine.
. . . . . blood pressure; — — — — — β lipoprotein; ———— α_1 lipoprotein; — — — — $-S(40-70)$; ——— — — $-S > 70$; ---------- α_2 lipoprotein.

II. ELECTROPHORETIC ANALYSIS

Method

Electrophoretic analysis of serum, plasma or serum lipoprotein concentrates was carried out by Longsworth's modification of the Tiselius method. Total protein concentration of serum or plasma was determined by Pregl modification of the Kjeldahl method.[7] When phosphate buffer, pH 7.8, is employed, electrophoretic analysis resolves the following components in order of decreasing mobility: albumin plus α_1, β, ϕ, γ globulin. The β-globulin complex is usually resolved as a double peak, the more rapidly migrating β_1, the slower β_2 globulin.

The electrophoretic mobility of the lipoproteins seems to be dependent on the relative amounts of amino acids in the molecule, the components with the higher nitrogen to lipid ratio exhibiting faster migration rates.

The pattern of the lipoprotein concentrates reported here obtained in the standard electrophoresis cell are similar to those obtained by paper electrophoresis of serum by Swahn[8] and by zone electrophoresis by Kunkel and Slater.[9]

TABLE 3.—*Ultracentrifugal Pattern of Serum Lipropotein Concentrate, Density 1.21, and Electrophoretic Pattern of Serum of Nephritics (Nephrotic Phase)*

No.	Date	$-S_{f,21}$ mg. per 100 ml. serum					Total Protein Gm./100 ml.	Albumen		α_2 globulin		β globulin		γ globulin		Cholesterol mg./100 ml.
		>70	40-70	30	23	4		Gm./100 ml.	%	Gm./100 ml.	%	Gm./100 ml.	%	Gm./100 ml.	%	
1	11/21/51	47	71	107	118+	237+	4.22	1.84	43.6	0.66	15.6	1.31	31.0	0.41	9.8	386
2		—	39	208+*	14	285+	5.03	2.32	46.0	1.43	28.4	0.85	16.9	0.44	8.8	372
3		—	117	286†	29	78	4.12	0.98	23.7	1.34	32.6	1.38	33.4	0.42	10.3	
4	2/9/51	91	239	260*	13	104	4.74	1.94	41.0	0.96	20.1	1.69	35.7	0.15	3.2	420
	5/14/51	52	88	195+*	26	99	4.62	1.91	41.2	0.96	20.9	1.36	29.5	0.39	8.4	406
	9/12/51	39	39	273+	20	156	4.66	2.52	54.0	0.81	17.4	1.01	21.6	0.32	7.0	321
5		—	24	200+†	59	192	5.09	2.06	40.6	1.58	31.0	0.94	18.4	0.51	10.0	545
6	5/18/51	78	162	228	360+	182	5.22	1.32	25.1	2.13	41.0	1.46	27.8	0.32	6.1	654
	10/10/51	18	68	130‡	300+‡	75	6.03	2.40	38.8	2.00	33.2	1.41	23.3	0.22	3.7	575
7	3/15/51	130	90	260+‖		138	5.75	0.92	16.0	1.40	24.4	3.06	53.1	0.37	6.5	1380
	5/7/51	78	47	234+‖		104	7.20	3.53	49.0	1.33	18.5	1.65	22.9	0.69	9.6	349
	6/29/51	—	23	208	34	156	7.83	4.65	59.4	1.00	12.8	1.31	16.7	0.87	11.1	257
	1/21/51	19	38	213+	19	142										
8	10/29/51	320+	128	140	395¶	88	3.73	0.72	19.5	2.32**	62.1	0.69	18.4(β_2)	—	—	430
9	4/19/51	78	156	130	260+	91	3.77	0.50	13.2	1.68	44.5	1.36	36.2	0.23	6.1	437
	8/22/51	260+	300	260+‖		34	3.26	0.33	10.0	1.92	58.9	0.79	24.4	0.22	6.7	643
	9/12/51	215+	237	151	279	34	3.85									612
10	5/7/51	390	240	104	364+	260	5.72	1.14	19.9	1.75	30.6	2.23	39.0	0.60	10.5	
	5/28/51	325+	260		325+‖	227	5.40	1.94	36.0	1.99	36.8	0.92	17.1	0.55	10.1	545
11	1/17/51						3.75	0.61	16.3	1.43	38.3	1.58	42.0	0.13	3.4	517
	7/30/51	390+	390	260	390+	185	4.09	0.88	21.6	1.67	40.7	1.46	35.7	0.08	2.0	1031
12	7/25/51	260+	78	185	52	156	6.55	3.65	55.7	1.51	23.1	0.98	15.0	0.41	6.2	385
	8/8/51	26	47	260+†	36	91	7.23	4.18	57.8	1.08	15.0	1.39	19.2	0.58	8.0	325
13	8/3/51	—	44	143	260+	65	3.47	0.38	10.9	2.07	59.8	0.92	26.4	0.10	2.9	808
N	8/29/51	39	81	130	182	130	4.93	2.12	43.0	1.10	22.3	1.08	22.0	0.46	9.3	469
14	4/18/51	31	78		325§	91	4.30	1.48	34.5	1.13	26.3	1.38	32.0	0.31	7.2	704
N.I.	10/10/51	50	118	225	325+§	117	3.82	1.38	36.1	1.16	30.4	1.04	27.3	0.24	6.2	550
	11/12/51	37	55	150	325+	75	3.87	1.27	32.7	0.84	21.8	1.38	35.6	0.38	9.9	698
15	8/2/51	52	78	91	208+	221	4.03	1.63	40.5	1.04	25.7	1.10	27.2	0.26	6.6	524
16	6/7/51	130	60	179†	13	133	4.99	2.71	54.4	0.95	19.0	0.95	19.0	0.38	7.6	286
	10/10/51	62	125	250+†	26	114	4.88	2.29	47.0	1.19	24.3	1.25	25.7	0.15	3.0	398

* −S 27
† double peak −S 32, 28
‡ Very broad peak
§ Double −S 23, −S 27. Broad peak, poorly resolved.
‖ −S(20–40) no resolution into definite peaks
¶ Double peak −S 20, −S 23
** No resolution of α_2 from β_1 globulin
N. Oral Nitrogen mustard; good response
N.I. Intravenous Nitrogen mustard 10/14, 10/15, 10/6.

Results

As had been observed previously[6] the electrophoretic serum protein pattern of patients with mild essential hypertension was normal. In patients with severe essential or malignant hypertension (76 cases) the β globulin was elevated (fig. 8) and the α_2 globulin showed a wider range of concentration than normal. Albumin was frequently decreased.

The electrophoretic pattern of the lipoproteins of serum of severe essential and malignant hypertensives concentrated by ultracentrifugation showed large amounts of α_2 and β globulin. The lipoproteins accounted for approximately 40 to 60 per cent of the total area of the β globulin and 30 to 40 per cent of the α_2 globulin fraction in the serum of nephrotics, and for 20 to 50 per cent of the β globulin and 15 to 40 per cent of the α_2 globulin in severe essential

or malignant hypertensives. In normal sera the lipoproteins were only 15 to 30 per cent of the β globulin area and 7 to 15 per cent of the α_2 globulin area. The increase in α_2 and β globulin concentration in severe essential and malignant hypertensive sera and in nephrotic sera is, therefore, largely accounted for by increased concentrations of lipoproteins.

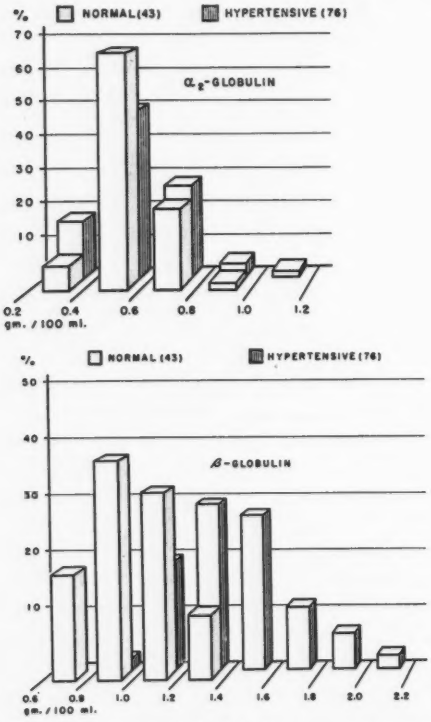

FIG. 8. The α_2 and β globulin concentrations in patients with severe essential and malignant hypertension, compared with normal human beings.

When studying the electrophoretic and ultracentrifuge patterns of lipoprotein concentrates, striking similarities were observed, which were emphasized by plotting the ultracentrifuge pattern on a flat base line (fig. 9).

The electrophoretic pattern of nephrotic serum lipoprotein concentrate exhibited clear α_1 and α_2 globulin peaks; the β_1 peak skewed to the slow side and additional slower migrating components corresponding to α_1, α_2, β and $-$S(40–70) components, respectively, of the ultracentrifuge pattern. The pattern of patients with essential hypertension showed α_1, α_2 and β_1 peaks, and in some a very small component trailing behind the β_1 lipoprotein, similar to those of normal sera. Malignant hypertensives usually had a component or components with migration rates less than that of β_1 lipoprotein and corresponding to comparatively large $-$S(40–70) and >70 components in the ultracentrifuge pattern.

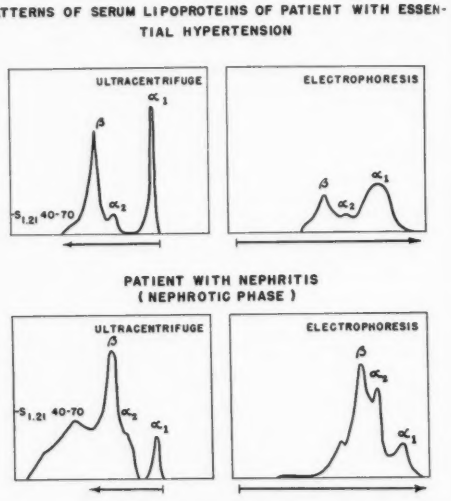

FIG. 9. Electrophoretic and ultracentrifugal patterns of lipoprotein concentrates of serum of an essential hypertensive patient and a nephritic (nephrotic phase) patient.

The sera of about 10 per cent of severe essential or malignant hypertensives were characterized by very poor resolution of the α_2 from the β globulin. After removal of the lipoproteins separation was sharp. The electrophoretic pattern of the lipoprotein concentrates was often poorly resolved, in part due to the fact that the mobility of the β lipoprotein was greater in both hypertensives and nephrotics than in normal lipoprotein concentrates. In the ultracentrifuge negative sedimentation of the β lipoprotein fraction was often slower than normal, approaching that of α_2 lipoprotein, being $-$S 25 to 27 instead of $-$S 30. α_2 globulin of normal sera has a negative sedimentation of about $-$S 23.

Discussion

The combined use of electrophoretic and ultracentrifugal analysis of serum has advantages over either one alone in that the information derived from both in many cases is additive rather than substitutive.

There are certain characteristics of the lipoproteins of normal serum which deserve comment. The $-S > 70$ component was usually greater in men than in women. This lipoprotein, if that is what it really is, which is very light, contains much chylomicron-like material, along with other lipids. Its neutral fat concentration is high. It probably represents fat in the early stages of its metabolism. The fact that it is greater in amount in plasma of men than of women has suggested that the preponderance of atherosclerosis in men might be in part due to this fact. As we have pointed out on numerous occasions before, we do not believe any one factor alone is responsible for the multifaceted mechanism of the genesis of atherosclerosis.

The earlier results of Lewis and Page[6] suggested a close relationship between the increased quantities of β globulin and the occurrence of vascular disease. This is not to say that vascular disease need always result when β globulin is elevated. Again, the contrast in the concentration of β lipoprotein ($-S$ 25–40) between male and female is important. Even in the younger males the concentrations were much increased over the concentration in the corresponding age group of females. In the older group the concentration in women and men became more and more alike. Taken as a whole, about twice as many males have β_1 lipoproteins greater than 250 mg. than females. The increased β lipoproteins plus increased $-S > 70$ both point to males as victims of future vascular disease.

As Gofman and co-workers[4] first suggested, the $-S(40–70)$ (i.e., S_f 10–20) may be a highly important fraction of plasma in relation to atherogenesis. They found a correlation between its elevation and coronary atherosclerosis in human beings. The ultracentrifugal analysis using the higher density potassium bromide medium also shows an increased number of males with this component greater than in females.

In contrast, women usually had greater concentrations of $-S(2–8)$, i.e., α_1 globulin, than men and they tend to be significantly greater in older women. The α_1 fraction, on the contrary, did not change as men got older.

The α_2 lipoprotein (i.e., $-S$ 20–25) was the most constant of all the fractions, being less than 20 mg. in most people regardless of age or sex.

To get some notion of the biochemical significance of these fractions, comparison during disease states has been made. Hypertensive patients are important in this relationship chiefly because atherosclerosis and hyperplastic arteriosclerosis are an integral part of the disease. It is usually from one or both of these that the patients die. Early in the disease the lipoproteins are normal, but as it progresses, a steady increase in $-S(40–70)$ and $-S(25–40)$ components occurs. The α_2 lipoproteins increased but to a lesser degree while α_1, in women at least, decreased.

Using alcohol fractionation, Barr observed[10] an increased α_1 lipoprotein in serum of patients following treatment with estrogens. Similar increases in the α_1 globulin were obtained by ultracentrifugation of some of these same sera in our laboratory. The difference in α_1 lipoprotein concentration observed in the serum of the two sexes may be due to hormonal action. There is also the possibility that the ratio of the α_1 lipoprotein – β lipoprotein concentration provides additional information on the state of dispersal of the plasma lipids not provided by concentrations of each alone.

Treatment of patients with malignant hypertension with pyrogens has proved useful in a number of patients, as pointed out several years ago.[11] Especially striking is the betterment of the necrotizing hemorrhagic arteriolitis. During treatment when fever occurs twice daily, the larger molecular lipoprotein aggregates increase greatly while the more dense α_1 fraction decreases. The α_2 fraction showed no significant change. When treatment was stopped, or the febrile reaction decreased due to development of tolerance, and clinical

improvement had occurred, all lipoprotein fractions tended to revert to pretreatment levels. We suppose that the increase in the less dense or larger molecular lipoproteins means either that the increased metabolism due to fever has demanded an increased turnover of lipid or, less likely, that the fever has slowed the passage of fats down the metabolic ladder to the lower molecular weight species. In any case, there seems to be no obligate relationship between this phenomenon and the resolution of the vascular disease except that it indicates a very active metabolism of tissue including blood vessels. That it is a metabolic event and not due to lowering of blood pressure is attested to by the failure of change when hypotensive drugs such as 1-hydrazinophthalazine or sodium nitroprusside are given.

The nephrotic syndrome has been associated in the minds of most clinicians with severe lipemia, indeed it has been called on occasion a lipid diabetes. Vascular disease of the atherosclerotic type is hastened by appearance of the syndrome. The utilization of fat appears to be normal; some abnormality in transport seems to be at fault. We suggested some time ago that the loss of protein in the urine without equivalent loss of lipid might account in part for the accumulation of lipid in the blood. The urine of these patients contains large amounts of protein with almost no lipid.[12]

As would be expected, the lighter, larger molecular weight $-S > 70$ and 40–70 components were increased. The β_1 lipoproteins were abnormal in their response to resolution and were much increased in concentration as found originally by Longsworth and MacInnes.[13] This fraction, as we have suggested, is often associated with developing vascular disease. The α_2 fraction is also greatly augmented in concentration. Thus all but the α_1 lipoproteins are sharply increased while the albumin and γ globulin are decreased. It is the albumin which makes up most of the protein in the urine of nephrotics. Failure of glomerular filtration or complete tubular reabsorption could account for the accumulation of lipoproteins with concurrent loss of albumin.

Thus, both in severe hypertensives and in nephrotics during periods when atherosclerosis tends to develop rapidly, lipoproteins are present in superabundance.

Lipoproteins in both diseases are greatly increased in concentration, but so are the lighter high molecular weight aggregates. It can only be said that chronic elevation of the β lipoproteins is a more unusual event, that elevation of the chylomicron-like fraction occurs temporarily with each fatty meal. The attribution of an exclusive atherogenesis to any one serum fraction is not justified from these or other studies.

Summary

1. Ultracentrifugal analysis of sera of normal, hypertensive and nephrotic human subjects was made, using a density of 1.21. Normal males had greater concentration of the $-S > 70$ fraction than females at all ages. The $-S(25–40)$ (i.e., β lipoproteins) was low in younger females, tending to rise with increasing age. In younger males this fraction was increased and almost equal to the concentration in females of the older age (34 to 60 years) group. The $-S(40–70)$ fraction (i.e., S_f 10–20 class of Gofman) was present in some instances in both sexes but much less in young females and slightly less in young males than in men and women of older groups. The $-S(20–25)$ (i.e., α_2) fraction was small and about equal in quantity in most normal people. The $-S$ (2–8) (i.e., α_1) fraction was more concentrated in women than in men; especially in the older women. In contrast this fraction did not change as men got older.

2. The concentration of α and β lipoproteins in early hypertension is normal for the corresponding age and sex. As hypertension becomes severe or malignant the $-S(40–70)$ (S_f 10–20), $-S(25–40)$ (β_1 lipoprotein) and $-S(20–25)$ (α_2 lipoprotein) increased. Patients with the most severe renal disease exhibited especially great increase in the $-S(40 - 70)$ and > 70 fractions.

3. During treatment of malignant hypertension with pyrogens a large increase occurs in the $-S > 70$, $-S(40–70)$ and β_1 lipoproteins. A marked decrease in α_1 lipoprotein, with no change in the α_2 fraction characterized the period of febrile reaction to the pyrogen.

The lipoprotein pattern reverted back to pretreatment patterns on discontinuing treatment. Other hypotensive drugs such as Apresoline and sodium nitroprusside did not produce similar lipoprotein changes.

4. The nephrotic phase of glomerulonephritis is characterized by great increase in the concentration of the $-S > 70$, 40–70 and β and α_2 lipoproteins, as resolved by ultracentrifugation. The electrophoretic pattern of serum lipoprotein concentrate as compared with normal serum concentrates showed large α_2 and β globulin components and additional components with electrophoretic mobility less than that of β_1 lipoprotein.

5. Lipoproteins are in great abundance during the periods when atherogenesis is rapid in patients with severe essential and malignant hypertension and the nephrotic phase of glomerulonephritis. Both the α_2 and β lipoproteins and the lighter higher molecular weight aggregates contribute importantly to this abundance.

ACKNOWLEDGMENT

We wish to thank Mr. Richard Wetzel for help with the statistical treatment of the data.

SUMARIO ESPAÑOL

Se han hecho estudios en individuos normales, hipertensos y nefróticos usando un método de ultracentrifugación que demuestra claramente los componentes lipoproteínicos α y β del suero. Hay diferencias notables en la distribución de las lipoproteínas entre diferentes edades y sexos. Durante las etapas de aterogenesis en hipertensos y nefróticos las lipoporteínas α_2 y β y los agregados livianos de peso molecular alto contribuyen significativamente a la superabundancia de lipoproteínas del plasma. La atribución de una aterogenesis exclusiva a cualquier fracción del plasma no nos parece a nosotros justificada de acuerdo a estos y otros estudios.

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Cardiac Output, Central Volume and Dye Injection Curves in Traumatic Arteriovenous Fistulas in Man

By GEORGE E. SCHREINER, CAPT., MC, NORBERT FREINKEL, CAPT., MC, JOHN W. ATHENS, CAPT., MC, AND WILLIAM STONE III, CAPT., MC

Although arteriovenous fistulas are frequent in wartime, few measurements of cardiac output have been carried out by direct methods. Analysis of the curve obtained after rapid injection of T-1824 shows the feasibility of this method in patients with arteriovenous fistulas. Such patients have elevated cardiac indices, enlarged central blood volumes and acceleration of peak and manifest recirculation times. The abnormalities are corrected by surgery. Diagnostic use of the dye curve is suggested.

IN 1897 Stewart[1, 2, 3] introduced the derivation of a flow measurement from an arterial dilution curve described during the first circulation. Since then, most theoretic features of the injection, the sampling and the calculation have been critically examined[4–10] and the use of T-1824 as the indicator in this method has been validated by comparison of the dye injection method with the direct Fick procedure,[11, 12, 13] the rotameter,[14] and by simultaneous studies with labeled albumin[15] and erythrocytes.[16] The accuracy of the method as now employed is largely contingent upon ability to delineate the downslope which is interrupted by recirculation.

Considerations of recirculation assumed primary importance when plans were made to employ the dye injection method in patients with traumatic arteriovenous fistulas. However, little information is available concerning the effect of abnormal vascular communications on the contour of the arterial dye curve.

The present study was undertaken to describe the effects of arteriovenous fistulas on the arterial dye curve with the hope of increasing information relative to both the fistula and the curve.

METHODS

All subjects were ambulatory young men. Arteriovenous fistulas resulted from direct trauma to blood vessels. Measurements were made from two to eight (mean, 3.7) months after wounding. Details of the technic may be found in a previous communication.[15] It involved rapid injection of T-1824 through a catheter into the subclavian vein, and collection of blood every two seconds from the femoral artery. Terms in which the curves are analyzed are defined as follows:

1. Appearance time: The interval from injection to the first sample containing dye. This compares with an ordinary point to point circulation time.

2. Upslope time: The interval from appearance of the dye to the attainment of maximum concentration.

3. Disappearance time: The duration of the extrapolated downslope from peak concentration to the base line.

4. Clearance time: The sum of 2 and 3. This is the theoretic time in which one central circulation would be cleared of dye if no recirculation occurred.

5. Appearance to manifest recirculation: The interval from first appearance of dye to the first point which deviates from the straight line of the downslope. This probably corresponds to the beginning of recirculation through shorter routes.

6. Peak to manifest recirculation: The interval from maximum concentration to this first deviation from the downslope.

7. Peak recirculation: The interval from the maximum concentration in the first circulation to the maximum concentration of the recirculation.

8. Plasma cardiac output (L.)

$$= \frac{\textit{Mg. dye injected} \times 60}{\textit{Mean concentration (mg./L.)} \times \textit{clearance time (min.)}}$$

9. Cardiac index

$$= \frac{\textit{Plasma cardiac output (liters)}}{(1 - \textit{hematocrit}) \times \textit{sq. M body surface area}}$$

From the Department of Surgical Physiology and Department of Biophysics, Army Medical Service Graduate School, Washington, D. C.

TABLE 1.—*Traumatic Arteriovenous Fistulas, Circulatory and Dye-Curve Data*

Diagnosis	Plasma Cardiac Output, cc./Kg.	Cardiac Index, L./min./M²	Appearance	Upslope	Disappearance	Clearance	Appearance to Manifest Recirculation	Peak to Manifest Recirculation	Peak Recirculation
			Time in seconds						
Control Group									
1. Student	52	3.41	12	6	22	28	16	10	18
2. Student	66	4.83	16	10	25	35	20	10	16
3. Thrombophlebitis	44	3.58	16	6	23	29	18	12	20
4. Peptic Ulcer	59	4.34	10	4	19	23	14	10	18
5. Frostbite	31	2.53	10	6	19	25	20	14	22
6. Hepatitis	41	2.60	16	12	24	36	20	8	24
7. Frostbite	43	2.99	16	6	23	29	20	14	20
8. Parotitis	60	4.8	14	12	11	23	22	10	18
9. Renal Calcinosis	55	4.23	14	6	22	28	16	10	18
10. Postganglioneurectomy	63	4.18	10	4	11	15	14	10	16
11. Ulcerative Colitis	72	4.62	10	6	10	16	14	8	16
Mean	53.3	3.83	13.1	7.1	19	26.1	17.5	10.0	18.7
A-V Fistula Preoperative									
Site									
1. R. Popliteal	89	6.91	7	7	10	17	15	8	12
2. R. Femoral*	—	—	9	—	—	—	—	—	—
3. R. Femoral	74	6.18	10	4	12	16	12	8	10
4. R. Carotid	71	4.47	11	7	23	30	15	8	10
5. R. Popliteal	128	8.44	11	5	11	16	15	10	14
6. R. Femoral	58	4.95	18	8	32	40	16	8	14
7. L. Femoral	55	4.43	10	8	22	30	14	6	10
Mean	79.2	5.90	10.8	6.5	18.3	24.5	14.5	8.0	11.7
A-V Fistula Postoperative									
1. L. Femoral	82	5.21	13	3	24	27	11	8	16
2. R. Femoral	38	3.58	14	6	19	25	18	12	20
3. R. Femoral	78	5.52	6	6	11	17	14	8	18
4. R. Subclavian	58	3.97	12	8	16	24	16	8	16
5. L. Femoral	72	4.34	11	7	12	19	19	12	22
6. R. Carotid	50	2.98	12	8	24	32	20	12	18
7. R. Carotid†	74	4.68	14	4	12	16	14	10	17
8. R. Popliteal	49	3.33	12	6	14	20	16	10	20
Mean	62.6	4.20	11.8	6	16.5	22.5	16	10	18.4
Mitral Stenosis									
Before Exercise	54.4	3.3	16	10	31	41	24	14	30
After Exercise	56	3.38	16	8	32	40	20	12	26

* Early recirculation prevented delineation of downslope.

† Spontaneous closure. See discussion.

10. Central volume[10] = $\frac{\textit{Cardiac output}}{\textit{Slope of descending limb}}$

These measurements are presented graphically in Figure 1, which shows one patient's dye curve before and after manual occlusion of a popliteal fistula.

RESULTS

Dye curves have been measured in seven patients with patent arteriovenous fistulas. Similar measurements were made in eight

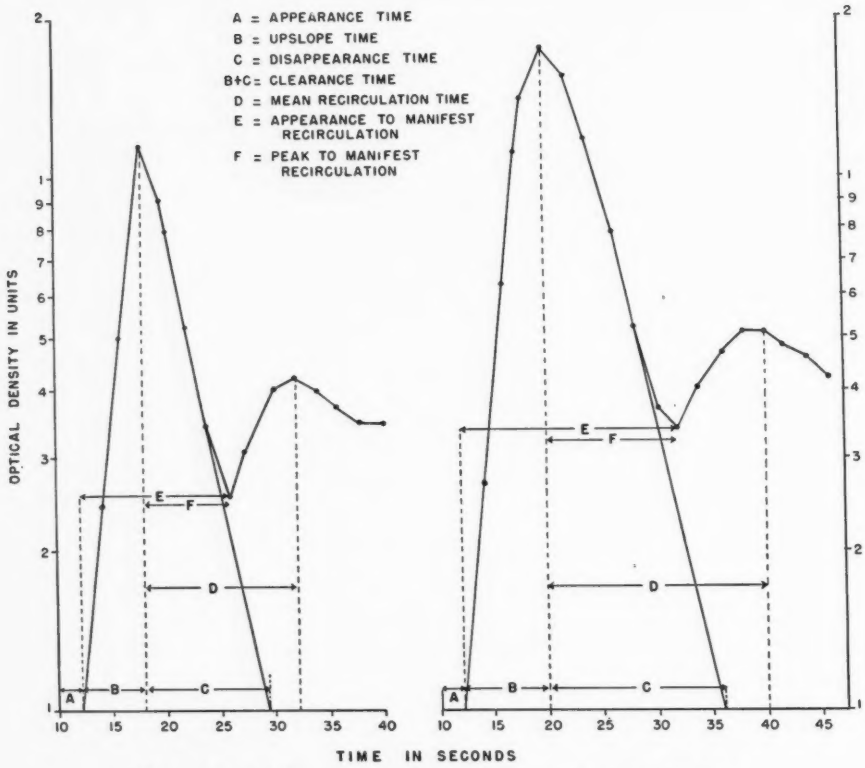

FIG. 1. Arterial dye curves. Right popliteal arteriovenous fistula.

patients after surgical repair of their fistulas. Two observations were made on a patient with rheumatic heart disease and moderately severe stenosis of the mitral valve. Eleven subjects served as controls.

Cardiac indices in six patients with fistula ranged from 4.4 to 8.4, and averaged 5.9. This is considerably above the mean of 4.2 for the postoperative group and 3.8 for the control group. The presence of an abnormal communication shortened the appearance time in only two individuals and did not alter the time required to reach a peak concentration and decline.

Although the appearance to manifest recirculation time was shortened, the acceleration amounted to only three seconds in the case of manifest recirculation as contrasted with seven seconds for peak recirculation. Thus, acceleration of the peak recirculation was the most significantly affected parameter. It ranged from 10 to 14 (mean, 11.7) seconds in the patients with fistulas; from 16 to 22 (mean, 18.4) seconds in the postoperative group; and from 16 to 24 (mean, 18.7) seconds in the control group. This represents an acceleration to less than two thirds of the control time and is significant as seen from the absence of any overlapping values. Peak recirculation was markedly prolonged in the patient with mitral stenosis although this could be accelerated by three minutes of elevated leg raising. Data are presented in detail in table 1.

In three patients, it was possible manually to occlude the arteriovenous fistula, and the dye injection was exactly repeated after one minute of occlusion. Data are summarized in table 2. Cardiac indices fell to 43, 72 and 70 per cent, respectively, of the initial value. Peak recirculation time lengthened strikingly from 14 to 20, from 10 to 20 and from 14 to 20

econds respectively. Postoperative observations obtained in two of these patients correspond closely with those obtained during manual occlusion. Curve contours of case I (table 2) are illustrated in figure 1 and of case II (table 2) in figure 2.

TABLE 2.—*Traumatic Arteriovenous Fistulas. Studies Related to Manual Occlusion*

Case Study		Cardiac Index 1	Appearance 2	Appearance to Manifest Recirculation 3	Peak Recirculation 4	Ratio Col. 3 / Col. 4
		L./min./M²	*Time in Seconds*			
I	A	8.44	11	15	14	1.07
	B	3.62	14	16	20	.8
	C	3.33	12	16	20	.8
II	A	4.47	11	15	10	1.50
	B	3.21	12	18	20	.9
	C	2.98	12	20	18	1.1
III	A	4.95	18	16	14	1.14
	B	3.45	18	16	20	.8

I. Rt. Popliteal Arteriovenous Fistula.
  A. Fistula open. Eight months after wounding.
  B. During manual occlusion for one minute preceding injections. Pulse diminished 8 beats/min.
  C. Three months after surgical repair of fistula.
II. Rt. Carotid—Jugular Arteriovenous Fistula.
  A. Fistula open. Three months after wounding.
  B. Manual occlusion. Pulse diminished 18 beats/min.
  C. Five weeks after surgical repair of fistula.
III. Rt. Femoral Arteriovenous Fistula.
  A. Fistula open. Two months after wounding.
  B. Manual occlusion. Pulse diminished 32 beats/min.

The central volume of Newman[10] was calculated in all these cases. Data are summarized in table 3.

TABLE 3.—*"Central Volumes"* $V = \frac{F}{S}$

Series	Subjects	ml. Average	Per cent of Blood Volume
A-V Fistula	6	1322	18.9
Control	16	720	13.3
Newman[20]	9	715	15

Discussion

Use of the dye injection method in the presence of an arteriovenous fistula might be challenged on theoretic grounds. Early recirculation through the shunt might be expected to alter the curve in many ways up to and including complete obliteration of the downslope.

It is apparent that peak recirculation is more rapid in all fistula patients. The critical limit

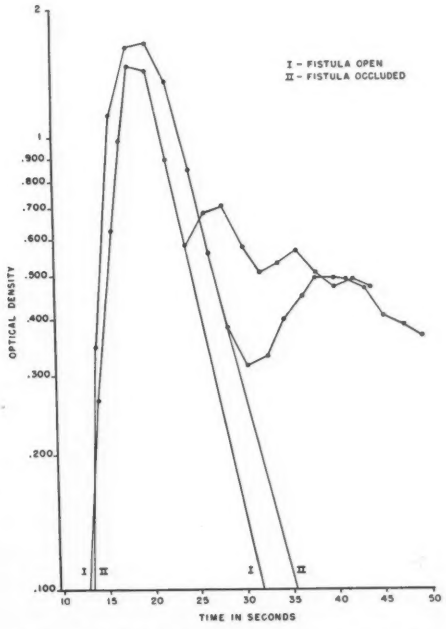

FIG. 2. Arterial dye curves. Right carotid-jugular fistula.

in the measurement of cardiac output by the Hamilton technic, however, is the appearance-to-manifest recirculation time. If manifest recirculation were shortened to the same extent as the peak recirculation time, only three to four seconds would remain to draw the downslope. However, it is seen that this manifest recirculation is shortened by an average of only three seconds.

The dissociation between the normal short circulations and the effect of a fistula on peak

recirculation may be seen by deriving the ratio:

$$\frac{\textit{Appearance to manifest recirculation}}{\textit{Peak recirculation}}$$

This ratio tends to be below unity in control subjects and above unity in fistula patients. It is seen in table 2 that manual occlusion in every case produced reduction in this ratio. Comparison may be made with the situation in mitral stenosis. After exercise, neither cardiac output nor appearance time changed, but both peak and manifest recirculation times shortened. The ratio was unchanged, (0.77 and 0.8). Thus, both short and long circulations participated proportionately in the acceleration of peripheral circulation which accompanied muscular exercise.

Sutton and his associates[9] have stated that recirculation tends to hide itself by contributing to the downslope and prolonging the time at which it should be manifest. If this mechanism were operating in the fistula patients, the slope of the descending limb would be smaller and the disappearance times would be falsely lengthened by the flattened curve. Instead, the slopes are either parallel or steeper, and the disappearance times tend to be shorter than in the control group. Downslopes, therefore, can usually be well delineated and the dye injection method loses little validity in the presence of a peripheral arteriovenous fistula.

Analysis of these curves may have a significant diagnostic value. Case 7 in the closed fistula series was referred with a pulsating mass in the neck, a thrill and loud bruit. The dye injection curve appeared relatively normal and the patient left the hospital on leave. On return, both thrill and bruit had disappeared and the patient had completed spontaneous closure of his carotid-jugular communication.

The increased cardiac output seen in these patients is in agreement with the reports of Warren, Nickerson and Elkin[17, 18] who used indirect methods. Some similar features in the dye curve contours may be found in the cuvette-oximeter tracings of Nicholson and co-workers[19] who studied congenital cardiac defects.

Summary

1. Analysis of the contour of the arterial dye curve has been carried out in control subjects, in patients with arteriovenous fistulas and in a patient with mitral stenosis.

2. The downslope can usually be well delineated in patients with arteriovenous fistulas and the validity of the dye injection method is supported.

3. Patients with arteriovenous fistulas show an elevated cardiac index, enlarged central volume and acceleration of both manifest and peak recirculation times.

4. Manual occlusion of the fistula produces a decrease in cardiac output and central volume, and a lengthening of both manifest and peak recirculation times. Manual occlusion curves closely resemble postoperative curves.

5. Diagnostic use of the dye curve is suggested.

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Sumario Español

Aunque fístulas arteriovenosas son epidémicas durante tiempo de guerra, pocas determinaciones de la producción total cardíaca se han obtenido por métodos directos. Analisis de la curva obtenida después de la inyección rápida de T-1824 demuestra lo factible que es este método en pacientes con fístulas arteriovenosas. Estos pacientes tienen índices cardíacos elevados, volumenes sanguíneos centrales agrandados y aceleración de tiempos máximos y de recirculación manifiestos. Las anormalidades son corregidas con la cirugía. Uso diagnóstico de la curva del tinte se sugiere.

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Studies of the Cerebral Circulation and Metabolism in Congestive Heart Failure

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In a study of the cerebral circulation and metabolism in congestive heart failure, using Kety's nitrous oxide technic, it was found that no significant alterations of the cerebral circulation were present when the quantities measured were compared with values determined for a control group. A decrease in cerebral blood flow and oxygen consumption below values established for normal young individuals was demonstrated to be secondary to the presence of arteriosclerosis and not to cardiac decompensation as had previously been concluded. It was also found that in the series studied the increased venous and cerebrospinal fluid pressures were not of sufficient magnitude to affect the cerebral circulation. The factor of a decreased arterial carbon dioxide tension as a cause for diminished cerebral blood flow in cardiac decompensation was similarly considered and dismissed.

THE INTRODUCTION of the nitrous oxide method[1] for the quantitative measurement of the cerebral circulation in humans has stimulated a renewed interest in the abnormalities of the cerebral hemodynamics and metabolism present in congesgestive heart failure. The earliest studies pertinent to this problem were the observations of Harrison,[2] who noted that in congestive heart failure the spinal fluid pressure is elevated to approximately the same extent as the venous pressure. It was further found that in such circumstances spinal fluid drainage results in a temporary improvement of orthopnea and dyspnea and a drop in the venous pressure. The implication of this study was that the cerebral circulation was aided by reducing the resistance offered by the increased intracranial pressure with consequent improvement of symptoms attributed to anoxia of the respiratory center.

The first application of the nitrous oxide technic to the actual measurement of the cerebral blood flow in cardiac decompensation resulted in a report that the cerebral blood flow is reduced 39 per cent below the normal.[3] The cerebral metabolism with respect to oxygen and glucose utilization was also found to be significantly reduced. This impairment of the cerebral metabolic rate was considered to result from an inability of the brain to increase its oxygen extraction from the blood in proportion to the drop in blood flow.

Scheinberg[3] inferred that the reduction in cerebral blood flow which he found was related to the 40 per cent reduction in cardiac output found by Stead[4] in a study of a series of patients with a similar degree of cardiac failure. However, the immediate mechanism producing a decreased cerebral blood flow was considered to be an intense cerebrovascular constriction. This was based upon the fact that a mean increase in the cerebrovascular resistance of 100 per cent above normal was found in the patients in congestive heart failure whose cerebral circulations were studied. An explanation for this increased cerebrovascular resistance was, however, wanting for lack of data relevant to the various factors influencing this quantity.

Perhaps the most important single factor in the intrinsic regulation of the cerebrovascular tone is the tension of carbon dioxide (pCO_2) in the blood. An increased arterial blood carbon dioxide tension has been shown to produce

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cerebral vasodilatation with a consequent increase in the cerebral blood flow.[5] Conversely, a decreased arterial blood carbon dioxide tension, such as could occur in the hyperventilation of heart failure, causes cerebral vasoconstriction and a decreased cerebral blood flow.[6] It is thus evident that a consideration of the carbon dioxide tension of arterial blood is essential to the understanding of any alteration of the cerebral hemodynamics.

Other physical factors which must also be considered as capable of contributing to an increased cerebrovascular resistance are the venous pressure in the internal jugular vessel and the cerebrospinal fluid pressure. In normal circumstances measurement of these quantities may be neglected. In congestive heart failure both are elevated, and their contributions to the production of increased cerebrovascular resistance must be evaluated. Although neither of these quantities was measured in the first report cited,[3] a more recent publication by Moyer and co-workers[7] mentions that the effect of the increased venous pressure may be considered negligible. These authors confirmed the presence of decreased cerebral blood flow (20 per cent) and an increased cerebrovascular resistance in the presence of congestive heart failure but found cerebral oxygen utilization to be normal. However, neither the blood carbon dioxide tension nor the cerebrospinal fluid pressure was measured in this investigation.

In addition to such physical and chemical changes which may be characteristic of congestive heart failure and thus responsible for the abnormalities of the cerebral hemodynamics and metabolism that have been found, another factor to be considered is the proper selection of controls for the purpose of comparing the parameters measured. In the previous studies cited,[3, 7] the values found for normal individuals were used to assess the changes found in cardiac decompensation. Such a procedure overlooks the possibility that deviations from the normal as observed in the presence of congestive heart failure may be a result of the very vascular abnormalities eventuating in the cardiac decompensation. In other words, the hypertension and/or arteriosclerosis responsible for the majority of the cases of congestive heart failure studied may have been responsible for the observed abnormalities rather than the heart failure itself being the principal causative factor. In an effort to eliminate this objection, we have used a control group composed of individuals with comparable vascular changes but lacking heart failure.

Methods

The cerebral blood flow was measured by the nitrous oxide technic of Kety.[1] The patients were in the fasting state and in the recumbent position.

Table 1.—*Clinical Status, Pulse, and Respirations of Patients with Congestive Heart Failure*

Subject	Age	Sex	Diagnosis	Pulse	Resp.	Mental State
A. F.	56	M	ASCVD	90	18	Clear
M. S.	63	M	CAHD	108	30	Clear
T. J.	50	M	HHD	108	15	Clear
A. C.	56	M	ASCVD	72	18	Clear
E. H.	58	F	CAHD	95	18	Clear
T. W.	45	F	HHD	112	21	Clear
E. N.	60	M	RHD	72	20	Clear
G. S.	78	F	ASCVD	96	15	Clear
H. F.	74	M	ASCVD	90	24	Clear
N. B.	72	M	ASCVD	90	24	Disoriented
L. M.	54	F	RHD	72	20	Clear
J. C.	63	F	ASCVD	100	20	Clear
J. Co.	56	M	PHD	80	24	Clear
D. N.	54	F	ASCVD	102	15	Clear
B. B.	72	F	ASCVD	132	20	Clear

Abbreviations: ASCVD—Arteriosclerotic cardiovascular disease; CAHD—Coronary artery heart disease; HHD—Hypertensive heart disease; RHD—Rheumatic heart disease; PHD—Pulmonary heart disease

The jugular venous pressure (JVP) was measured with a spinal fluid manometer, using the level at which the vessel was entered as the reference point. The brachial venous pressure (BVP) was measured in an antecubital tributary with a spinal fluid manometer, the reference level being a plane 5 cm. posterior to the plane of the sternal angle of Louis. The mean arterial blood pressure (MABP) was measured in a femoral artery using a damped mercury manometer. The cerebrospinal fluid pressure (CSFP) was measured in the lumbar region in the supine position, using either a spinal fluid manometer or a Statham strain gage manometer. The reference level used was a plane 3.5 cm. above the mattress on which the patient was lying. The oxygen and carbon dioxide contents of the venous and arterial blood were determined by the method of

Van Slyke.[8] Blood pH was determined anaerobically at room temperature, using a glass electrode. The values were corrected to body temperature by the method of Rosenthal.[9] The carbon dioxide tensions of arterial and venous blood samples were determined by the use of standard nomograms.[8] Blood glucose was determined by the method of Somogyi and Nelson.[10] The cerebral metabolic rate with respect to oxygen utilization ($CMRO_2$) was calculated by multiplying the cerebral blood flow by the arteriovenous oxygen difference. The cerebral metabolic rate with respect to glucose utilization (CMRGl) was calculated by multiplying the cerebral blood flow by the arteriovenous glucose difference. The cerebrovascular resistance (CVR) was calculated by use of the formula: $CVR = P/CBF$, in which P represents the difference between the mean arterial blood pressure and the jugular venous pressure, each expressed in mm. Hg.

Material

Table 1 presents in outline form a brief summary of the important clinical features of the cases studied. The majority of the patients were in the sixth or seventh decades, the mean age being 60. There were eight males and seven females. Of the 15 cases, eight patients were diagnosed as having arteriosclerotic cardiovascular disease, two each as having coronary artery heart disease, rheumatic heart disease, and hypertensive heart disease, and one as having pulmonary heart disease. All patients were in early phases of therapy for congestive heart failure. None was terminal, but all had, at the time of the study, continuing evidence of cardiac decompensation such

TABLE 2.—*Cerebral Hemodynamics and Metabolism in Congestive Heart Failure*

Subject	MABP	BVP	JVP	CSFP	CBF	CVR	CMR_{O_2}	CMR_{Gl}	R.Q.
A. F.	81	75	58	200	45	1.7	3.5	5	0.98
M. S.	86	—	80	220	34	2.4	3.2	—	0.94
T. J.	149	150	78	260	41	3.5	2.9	2	1.01
A. C.	120	125	194	350	50	2.1	2.9	4	0.95
E. H.	117	90	52	195	42	2.7	1.3	—	0.96
T. W.	165	—	159	300	53	2.9	3.8	—	0.93
E. N.	98	—	155	260	49	1.8	3.9	—	0.81
G. S.	90	90	90	205	27	3.1	1.9	4	0.90
H. F.	115	118	80	230	34	3.2	2.6	7	0.97
N. B.	83	—	75	330	37	2.1	3.1	—	1.01
L. M.	70	210	220	350	25	2.2	2.4	3	0.92
J. C.	143	39	128	250	25	5.4	2.2	4	0.94
J. Co.	90	130	184	150	36	2.1	2.3	8	0.97
D. N.	110	100	136	300	44	2.3	1.7	11	0.88
B. B.	130	78	110	230	57	2.1	3.1	2	0.85
Mean	110	111	120	255	40	2.6	2.7	4.5	0.93
S.E.	±7.2	±13.7	±13.7	±15.5	±2.6	±0.24	±0.20	±0.91	±0.017
p	>.05	<.01	<.02	<.02	>.1	<.05	>.5	>.5	>.9
"Controls" (18)									
Mean	95	61	80	202	48	2.0	2.9	6.2	0.92
S.E.	±2.4	±3.3	±6.9	±15.0	±4.0	±0.15	±0.27	±2.5	±0.25
"Normals" (12)									
Mean	91*	70*	103	202*	53*	1.8	3.4	6.5	0.98
S.E.	±3.0	±8.8	±8.8	±17.5	±5.0	±0.23	±0.15	±1.2	±0.034

ABBREVIATIONS: MABP: Mean arterial blood pressure, mm. Hg; BVP: Brachial venous pressure, mm. H_2O; JVP: Jugular venous pressure, mm. H_2O; CSFP: Cerebrospinal fluid pressure, mm. H_2O; CBF: Cerebral blood flow, cc./100 Gm./min.; CVR: Cerebrovascular resistance, mm. Hg/cc./100 Gm./min.; CMR_{O_2}: Cerebral metabolic rate, oxygen utilization, cc./100 Gm./min.; CMR_{Gl} Cerebral metabolic rate, glucose utilization, mg./100 Gm./min.; R.Q.: Cerebral respiratory quotient; S.E.: Standard error; p: probability of chance occurrence; $p < .05$ considered significant.

* Statistically significant difference from value found in congestive heart failure.

as dyspnea, orthopnea, basal rales, peripheral edema, serous effusions, congestive hepatomegaly, and elevated venous pressure. The presence of an elevated venous pressure generally separates those with predominantly right heart failure from those with predominantly left heart failure. All patients with the exception of N. B. were mentally clear at the time of the study.

and 76, the mean age being 62. All had evidence of the presence of systemic arteriosclerosis but none was in congestive heart failure. No cases with a mean arterial blood pressure above 115 mm. Hg were included. The "normal" group included only individuals under the age of 40.

TABLE 3.—*Blood Constituents in Congestive Heart Failure*

Subject	AO_2	ACO_2	ApH	$ApCO_2$	AGl	VO_2	VCO_2	VpH	$VpCO_2$	VGl	$(A\text{-}V)O_2$	$(A\text{-}V)$ CO_2	(A-V) Gl
A. F.	20.93	45.17	7.43	37	168	13.21	52.88	7.34	48	156	7.72	7.41	12
M. S.	19.39	37.59	7.32	38	—	9.90	46.51	7.24	50	—	9.49	8.92	—
T. J.	17.94	42.74	7.43	33	67	10.98	49.77	7.40	40	63	6.96	7.03	4
A. C.	15.56	46.49	7.34	44	107	9.81	52.07	7.30	53	100	5.75	5.58	7
E. H.	15.06	49.47	7.32	48	—	12.00	52.40	7.28	55	—	3.06	2.93	—
T. W.	15.65	44.52	7.62	24	—	8.41	51.28	7.55	29	—	7.24	6.76	—
E. N.	21.16	45.04	7.46	34	—	13.25	51.50	7.35	47	—	7.91	6.46	—
G. S.	15.27	54.62	7.38	47	100	8.27	61.92	7.32	60	85	7.00	6.30	15
H. F.	16.93	49.40	7.35	46	103	9.21	56.87	7.29	58	98	7.72	7.47	8
N. B.	20.06	44.01	7.46	35	—	11.61	52.55	7.31	53	—	8.45	8.54	—
L. M.	17.74	41.85	7.40	36	65	8.07	50.76	7.33	45	55	9.67	8.92	10
J. C.	17.27	48.71	7.33	47	78	8.50	56.96	7.29	55	63	8.77	8.25	15
J. Co.	17.35	33.13	7.33	33	250	10.91	39.35	7.26	41	227	6.44	6.22	23
D. N.	14.73	49.26	7.27	53	247	10.93	53.56	7.22	60	223	3.80	4.30	24
B. B.	20.10	52.67	7.33	52	92	14.65	57.27	7.30	58	88	5.45	4.60	4
Mean	17.68	45.65	7.39	40	128	10.65	52.36	7.32	50	116	7.03	6.58	12
S.E.	±0.57	±1.43	±0.01	±2.1	±22	±0.53	±1.58	±.03	±2.3	±20	±0.49	±0.45	±2.3
p	>.1	>.5	>.2	>.05	>.3	>.3	>.8	>.7	>.3	>.5	>.05	>.1	>.6
"Controls" (18)													
Mean	16.47	46.97	7.35	45	103	9.76	52.63	7.31	53	102	6.03	5.62	15
S.E.	±0.65	±1.33	±0.04	±1.9	±11	±0.82	±1.47	±0.03	±2.3	±13	±0.30	±0.37	±6.2
"Normals" (12)													
Mean	16.12	47.12	7.36	43	87	9.55	53.59	7.32	49	75	6.57	6.47	14
S.E.	±0.77	±1.37	±0.03	±1.5	±13	±0.82	±1.23	±0.04	±1.9	±12	±0.32	±0.45	±1.8

ABBREVIATIONS: A: Arterial (femoral); V: Venous (internal jugular); O_2: Oxygen content, vol. %; CO_2: Carbon dioxide content, vol. %; pCO_2: Partial pressure of carbon dioxide, mm. Hg; (A-V): Arteriovenous difference; Gl: Glucose content, mg. %.

RESULTS

Table 2 presents in detail the results obtained in a study of the various parameters concerned with the cerebral hemodynamics and metabolism in the 15 cases of congestive heart failure and, for comparison, a summary of the results obtained in this laboratory in a series of 18 cases classified as "controls" and 12 cases classified as "normal." The control group consisted of individuals between the ages of 50 Most of these patients were suffering from functional ailments or were convalescing from acute infectious diseases. No hypertensives were included in this group.

The mean arterial blood pressure of 110 mm. Hg for the congestive heart failure series is slightly but significantly higher than the mean value of 95 mm. Hg and 91 mm. Hg observed in the "control" and "normal" groups respectively. This value is not, however, above the

value of 115 mm. Hg which we arbitrarily use to separate normotensives from definite hypertensives.

The mean brachial venous pressure of 111 mm. H_2O is significantly higher than the mean values of 61 mm. H_2O for the "controls" and 70 mm. H_2O for the "normals." Similarly, the mean jugular venous pressure of 120 mm. H_2O and the mean cerebrospinal fluid pressure of 255 mm. H_2O for the congestive heart failure group are both significantly higher than the respective values for the "control" group which are 80 mm. H_2O and 202 mm. H_2O. Although the jugular venous pressure of the decompensation group is higher than the mean value of 103 mm. H_2O for the "normals," the difference is not statistically significant. The mean cerebrospinal fluid pressure of the failure group is, however, significantly higher than the mean value of 202 mm. H_2O for the "normals."

Coming now to the important quantity of cerebral blood flow, the value of 40 cc. per 100 Gm. per minute in congestive heart failure is not significantly lower than the mean of 48 cc. per 100 Gm. per minute for the "control" group. The former value is, however, significantly below the mean normal value for the cerebral blood flow of 53 cc. per 100 Gm. per minute. The same relationship is seen to hold in a comparison of the mean values for the cerebral metabolic rate (oxygen); that is, 2.7 cc. per 100 Gm. per minute (congestive heart failure) does not differ significantly from the "control" mean of 2.9 cc. per 100 Gm. per minute, although it is significantly lower than the "normal" mean value of 3.4 cc. per 100 Gm. per minute.

A significant increase of the cerebral vascular resistance in congestive heart failure is noted when the mean value of 2.6 mm. Hg per cc. per 100 Gm. per minute is compared with the "control" value of 2.0 mm. Hg per cc. per 100 Gm. per minute and the "normal" mean of 1.8 mm. Hg per cc. per 100 Gm. per minute.

No significant differences in the cerebral metabolic rate (glucose) or the cerebral respiratory quotient are noted among the three groups compared.

Table 3 summarizes the values obtained for the various blood constituents of the three groups. Without repeating the individual values noted in the table, it is sufficient to point out that there are no significant differences among the three groups for any of the quantities measured.

Discussion

The results of this investigation indicate that moderate heart failure in itself does not significantly lower the cerebral blood flow below the level found in the presence of arteriosclerosis without heart failure. The mean value for the cerebral blood flow of 40 cc. per 100 Gm. per minute in the failure group does not differ significantly from the value of 48 cc. per 100 Gm. per minute in a control arteriosclerotic group. The fact that there is a difference, albeit not a statistically significant one, may be attributed to errors of random sampling and the probable existence of a severer degree of arteriosclerosis in the failure group than in the "control" group. Such reduction of the cerebral blood flow that is observed is principally a function of organic occlusive changes in the cerebral vasculature of a group at this age level and is not directly caused by congestive heart failure. The finding by Moyer and associates,[7] using similar technics, of a cerebral blood flow of 45 cc. per 100 Gm. per minute in congestive heart failure as compared to their normal of 53 cc. per 100 Gm. per minute is in close agreement with our own observations. The significance of their findings, as would be true of our own, is misinterpreted without reference to a proper "control" group such as we have presented. The absolute values reported by Scheinberg[3] are not strictly comparable to our own because of differences in technic used.

The reduced cerebral metabolic rate (oxygen) noted in the failure series is also related to the presence of older age and arteriosclerosis rather than to the presence of cardiac decompensation. Both failure and "control" groups show an approximately 20 per cent reduction of the cerebral metabolic rate (oxygen) below the normal value of 3.4 cc. per 100 Gm. per minute. The exact significance of this reduced metabolic rate in the presence of arteriosclerosis is not immediately apparent, although an excellent correlation exists between the reductions from

normal of the cerebral blood flow and the cerebral metabolic rate in respect to oxygen (correlation coefficient, 0.75). Our results also fail to reveal a significant depression in glucose utilization in either the "control" arteriosclerotic group or the failure group. These relationships are discussed more fully elsewhere.[11]

On first inspection of the results, it would appear that there actually is an increased cerebral vascular resistance in the presence of congestive heart failure. The value of 2.6 mm. Hg per cc. per 100 Gm. per minute is significantly higher than the "control" value of 2.0 mm. Hg per cubic centimeter per 100 Gm. per minute. However, it must be recalled that an increased cerebral vascular resistance without concomitant change in the cerebral blood flow is a characteristic pattern in essential hypertension.[12] If the cerebral vascular resistance of the failure group is recalculated after eliminating the seven instances in which the mean arterial blood pressure is above 115 mm. Hg, a value of 2.2 mm. Hg per cubic centimeter per 100 Gm. per minute is obtained, and this does not differ from the "control" value. It is thus seen that it is unnecessary to implicate changes in the arterial carbon dioxide tensions in order to explain an increased cerebral vascular resistance in congestive heart failure, for there actually is no increased cerebral vascular resistance attributable to the failure, per se.

As implied in the foregoing discussion, no differences among the mean values for the arterial carbon dioxide tension in the three groups compared were found. Furthermore, no correlation was found between the arterial carbon dioxide tension and the cerebral blood flow in the failure series. Thus, whatever instances of a reduced cerebral blood flow were found accompanying congestive heart failure, could not be related to a decreased arterial carbon dioxide tension.

The presence of an elevated venous pressure, both brachial and jugular, and an elevated cerebrospinal fluid pressure are to be expected in the presence of congestive heart failure, and our series is no exception. A general parallelism between the degree of elevation of the venous pressure and the cerebrospinal fluid pressure has been previously noted[2] and is confirmed in our data. The degree to which an elevated cerebrospinal fluid pressure might be responsible for an increased cerebral vascular resistance and a decreased cerebral blood flow in this series is probably negligible. Kety, Shenkin, and Schmidt[13] have demonstrated that the cerebrospinal fluid pressure must exceed the critical level of 450 mm. H_2O before the cerebral blood flow is significantly reduced by increased intracranial tension. Certainly, however, we cannot exclude the possibility that in isolated cases such values are obtained and may thus contribute to cerebral circulatory insufficiency with resultant mental changes. Similarly, although we are unable to correlate decreases in cerebral blood flow and increases in cerebral vascular resistance with the magnitude of the venous pressure elevation or the severity of the failure as judged clinically, we cannot exclude the existence of a critical level for the cardiac output below which the cerebral circulation is embarrassed. Reason would lead us to believe that this probably is the case. However, in a limited series such as has been studied, such factors as degree of failure, height of cerebrospinal fluid pressure and height of venous pressure are of little significance in the etiology of such changes as were found. The general absence of mental symptoms among the failure cases studied precludes the drawing of conclusions concerning the relationship of changes in cerebral blood flow and the cerebral utilization of oxygen to the occurrence of alterations of consciousness or personality. However, as has been implied, in extreme cases of congestive failure, such mental aberrations could be attributed to any or all of the various mechanisms enumerated.

On a purely teleologic basis, what has been demonstrated by actual measurement, the tendency for the cerebral circulation to be maintained in spite of a decreasing cardiac output, might well have been predicted. One would expect such protection to be afforded to the circulation of an organ so sensitive to anoxic and anemic changes as is the brain. Investigation has shown a similar relationship to hold for the coronary circulation in congestive heart failure. Both coronary blood flow

and myocardial oxygen utilization are maintained in the face of marked decreases in the cardiac output.[14] On the other hand, the hepatic flow is decreased in proportion to the drop in cardiac output,[15] and the renal blood flow is decreased to a much greater extent than is the cardiac output.[16] From these various studies there thus emerges a basic physiologic pattern: the redistribution of a reduced cardiac output in congestive failure in such a way as to preserve the circulation of the two organs most essential for immediate survival, the heart and the brain.

Summary

1. The cerebral blood flow, metabolism, and vascular resistance have been studied in a group of 15 patients with moderately congestive heart failure. No significant differences were found when the respective values were compared with values obtained for a control group.

2. The cerebral oxygen utilization and blood flow in congestive heart failure were found to be significantly reduced below values established for normal young individuals, but these changes were demonstrated to be a function of increasing age and arteriosclerosis and not of congestive heart failure.

3. Both internal jugular venous pressure and cerebrospinal fluid pressure were found to be elevated in cardiac decompensation. These elevations were of similar magnitudes, but in no instance in the series studied was the degree of elevation of either quantity sufficient to adversely influence the cerebral circulation.

4. Measurement of arterial carbon dioxide tension failed to reveal instances of a reduced cerebral blood flow which could be attributed to a reduced arterial carbon dioxide tension.

5. It is concluded that in congestive heart failure there is a tendency for the cerebral blood flow and metabolism to be maintained in the face of a diminished cardiac output, although the possibility of cerebral circulatory embarrassment in extreme degrees of failure has not been excluded and is even considered quite likely.

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Sumario Español

En un estudio de la circulación y metabolismo cerebral en decompensación cardíaca, usando la técnica de Kety con óxido de nitrógeno, se encontró que no hubo alteraciones significantes en la circulación cerebral cuando las cantidades medidas fueron comparadas con valores obtenidos en un grupo control. Un decremento en circulación cerebral y consumo de oxígeno bajo los niveles establecidos para sujetos jovenes normales se demostró ser causado por la presencia de arterioesclerosis y no debido a decompensación cardíaca como previamente se había concluído. También se encontró en la serie estudiada que el aumento en presión venosa y cerebroraquídea no fué de suficiente magnitud como para afectar la circulación cerebral. El factor de reducción en la tensión del bióxido de carbono arterial como una causa en el decremento en circulación cerebral en decompensación cardíaca fué similarmente considerado y eliminado.

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Calibration of the Direct Ballistocardiogram

By T. J. Reeves, M.D., Kathryn Willis, M.D., Earnest Booth, M.D., and Haskell Ellison, M.D.

A simple method of calibrating the amplitude of the direct ballistocardiogram, utilizing a standard external force to the body, is described. Such a method tends to neutralize many of the variables in apparatus alignment and sensitivity, and provides a basis for comparison of amplitudes in the same and different subjects. Normals of different age groups were studied and the contrast with abnormals with known cardiovascular disease is shown.

THE QUESTION of the relative advantages and disadvantages of the several technics for recording the motions of the body subsequent to the forces of the cardiac cycle remains unsettled. However, the simple methods for recording these motions directly from the body, as described by Dock and Taubman,[1] are becoming widely used clinically for the obvious reasons of mobility, economy, and simplicity.

One of the valid objections to the use of these technics has been the lack of a calibration procedure whereby the records made at one time on a subject may be compared quantitatively with subsequent records made on the same subject. The lack of calibration also makes it impossible to compare the amplitudes of the various deflections from subject to subject, although Starr and others have suggested that the matter of amplitude may be of significant diagnostic and prognostic import.[2, 3]

The initial publications of Dock and Taubman[1] described a pendulum delivering a standard blow to the subject as a method of calibration. Detailed data were not presented, however, and subsequent reports by these and other authors have failed to clarify this problem. Moreover, some of the commercially available direction manuals[4] for "Direct Ballistocardiographs" suggest only a standard sensitivity of the recording apparatus to a known signal input, for example 1 cm. per 1 mv., as the method of comparative calibration. That this method is invalid will be demonstrated below.

Of the various devices used at present to transform the body motion into recordable electrical energy, the ones most widely used are: (1) the electromagnetic method, (2) the photoelectric method, and (3) the piezoelectric method. Instruments based on these methods are commercially available. Although the different instruments vary to some extent in the type of information given, they all suffer from the same disadvantage of being difficult to *restore* to a given point of sensitivity, and are thereby prone to give different amplitudes at various times for identical body motion, whether it be recorded as displacement, velocity, or combinations. It should be emphasized that this variation lies in the transducer and not in the recorder, per se.

This difficulty arises chiefly from the fact that there is a narrow range of recording fidelity, as regards amplitude, allowable in the positioning of the generating components, that is, in the magnet-to-coil relationship, the photocell-to-light beam portion, and the tension of the ceramic in the piezoelectric method. In other words, a minute change in the relative positions of the generating components will cause major change in amplitudes of the deflections of the ballistocardiogram, though the "string sensitivity" of the recording device remains constant (fig. 1). In addition, when these records are made on a standard electrocardiograph recorder without a preamplification attenuator, the string sensitivity must

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e kept very low. At a subsequent time it is difficult to restore this sensitivity precisely, nd in some subjects changes of 1 mm. per av. input result in significant change in mplitude. Thus it is evident that even if these nstruments are calibrated in absolute units millimeters per second or millimeters per displacement, etc.), such calibration is valid nly if the knife-edge relationship of the gen- rating components of the transducer is onstantly maintained. Such precise main- tenance is difficult, if not impossible, with the presently available apparatus.

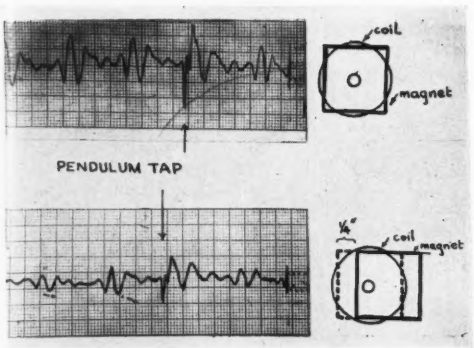

FIG. 1. Tracings on same subject, with string sensitivity constant, showing decrease in amplitude when magnet to coil relationship is altered by one-quarter inch. Note that ratio pendulum amplitude to ballistocardiogram amplitude remains constant.

Smith[5] has recently adapted a bar magnet velocity meter, devised by Perls,[6] to clinical ballistocardiography. This device has a much greater tolerance in magnet-to-coil relationship, can readily be calibrated in quantitative units, and has a flat frequency response (amplitude) beyond the range encountered in ballistocardiography. Unfortunately, this device is not yet in use by other investigators or clinicians.

The difficulty in comparison of ballistic amplitudes from subject to subject with the direct technics, lies in the fact that different individuals vary considerably in the factors of tissue elasticity, body mass, and surface contacts, so that the response in terms of body motion to a similar force will vary from subject to subject. It has been our experience that *normal* subjects will show a wide range of amplitudes if a standard recording sensitivity is used, even with subjects of essentially the same body mass and general build.

The principle of using a standard external force, such as the Dock-Taubman pendulum,[1] to produce a motion of the body which can be recorded at any desired amplitude, seemed to apply to both of the major sources of calibration difficulties. Thus, recording the motion of the body resulting from a standard force at any desired level, regardless of the actual sensitivity of the recording string, should overcome the transducer problems. Similarly, if the deflection to a standard force is recorded as the same amplitude in different subjects, the differences in body mass and suspension should be equalized. The practical application of this method was, therefore, investigated.

METHOD

The pendulum used by Dock and Taubman[1] was a padded lead weight of 220 Gm. on a 12 cm. arm with a fixed arc of swing, delivering an impact to the shoulder of the subject. However, the motion at the body resulting from such a tap varies according to the distance of the impacted spot from the longitudinal axis of the body and the torsion thereby produced. This factor was apparently of major importance in early experiments on cadavers in the laboratory, in causing difficulty in obtaining the same deflection from the pendulum on the same subject when repeated at short intervals. The torsional effect also caused "splintering" of the deflection, with resultant difficulty in measurement. It was found that these difficulties were of much less note when the impact was delivered to the head of the cadavers in the longitudinal axis of the body. The point of impact was fixed at approximately the junction of the posterior and middle third of the skull in the midline, to minimize either lateral or dorsoventral torsion.

Since any form of padded lead or wooden weight was found to result in pain to the head of the subject, a less traumatic weight was sought for the pendulum. It was found that a standard rubber handball* of 300 Gm., when affixed to an aluminum tubing arm of one fourth inch diameter, 16 inches in length with a metal thickness of one sixteenth inch, and having a 45 degree arc of swing (fig. 2), gave a painless tap to the head resulting in a pendulum deflection of slightly greater amplitude than the I-J

* Standard American Athletic Association, 2 inch diameter handballs are manufactured by A. G. Spaulding Company and are available at most sport goods stores.

stroke of the ballistocardiogram of young normal subjects. It was determined that adding weights of 5 to 10 Gm. to the handball had no appreciable effect on the resultant pendulum deflection, but that added weights of 20 Gm. or more resulted in an increase of significant degree. It was also determined that reasonable variations in elasticity of the ball had little significant effect on the deflection, since a handball in use for six months gave the same deflection as an obviously more resilient new ball of the same weight. Two different pendulums, using separate handballs of similar weight, were found to give similar deflections. It was determined that variations of two inches in the distance of the

FIG. 2. Photograph of pendulum used in calibrating direct ballistocardiogram.

pendulum stand from the head had no significant effect on the pendulum deflection, nor did variations of two inches dorsoventrally of the point of impact on the head. However, if the point of impact was moved laterally, far enough to produce a glancing rather than a "solid" blow, significant variations occurred.

The transducer used for recording the body motions was the electromagnetic device, as previously described by Dock.[7] The recording instrument was the multichannel Cambridge Simpliscribe. Simultaneous carotid pulses were recorded, using a glycerine capsule with a crystal transducer. The procedure of calibration on all subjects was as follows:

Using the pendulum described above, with a subject at standard conditions of rest on the table, the pendulum was adjusted to the head so that with the weight hanging plumb, it just touched the scalp. If hair was present, light finger pressure was used to move the ball into juxtaposition with the scalp. The pendulum arm was aligned with the nose to achieve centering in the sagittal plane. The head support consisted of a notched wooden block lined with foam rubber of one-inch thickness. This was utilized to prevent head turning and alteration of the point of impact. The feet were supported in a similarly notched and lined block, for the sake of comfort and to maintain the transducer in relatively constant relationship. The effect of the lining and table surfaces will be discussed in a subsequent communication. With the recorder running, the pendulum was released manually from the 45 degree position and timed to strike in late diastole, at which time the body motion is minimal. With practice this can be accomplished readily. Only those deflections occurring at such times were measured. The factor of careful timing is less important with subjects having low-amplitude ballistocardiograms, because the pendulum force is considerably greater than force of body motion. The sensitivity of the recorder may then be adjusted to give any desired amplitude to the deflection resulting from the pendulum force. It has been found that with normal subjects, when the pendulum deflection is recorded as 20 mm., the amplitude of the ballistocardiograph complexes in normal subjects will be at a convenient range.

RESULTS

1. The first problem was to determine the validity of this method as a means of setting the sensitivity of the apparatus to a given level, so that the ballistocardiograms of the same individual could be compared quantitatively at different times. If the method were valid, then the ballistocardiograms of normal subjects under standard conditions should have approximately the same amplitude from time to time.

Using the technic described above, ballistocardiograms were made on six normal subjects on two days, at least one week apart. They were made one hour or more after the last previous meal, and after a period of 15 minutes' rest on the table. No smoking was allowed during this period. The records were made during quiet respiration. Tracings were made at a recording sensitivity such that deflection subsequent to the pendulum force (pendulum deflection) was approximately 20 mm. amplitude. The ballistic systolic waves were then measured for seven consecutive cardiac cycles, and the range and average of each recorded. An average of three satisfactory

pendulum deflections was taken as the pendulum deflection. If the pendulum deflection was not exactly 20 mm., each of the systolic waves (HI, IJ, JK) was then "corrected" to a pendulum deflection of such an amplitude by a proportional equation relating the measured pendulum deflection and a measured ballistic deflection to the desired pendulum deflection.

TABLE 1.—*Comparison of Systolic Deflections of Ballistocardiograms from the Same Subject Made on Different Days, Calibrated with a Standard Pendulum Impact*

Normal Subjects		Pendulum Amplitude		HI Amplitude		IJ Amplitude		JK Amplitude	
		Day I	Day II	Day I	Day II	Day I	Day II	Day I	Day II
K. W.	R*	17–18	22–23.5	4–6	4–8	8.5–10.5	10–14.5	7–10	11–14
	A†	17.3	22.3	5.6	6.4	9.4	12.7	8.2	13.2
	C‡	20	20	6.4	5.7	10.9	11.4	9.4	11.7
R. G. T.	R	20–21	20–21	5–9	5–7	10–16	10.5–14	11–13	13–15.3
	A	20.7	26.7	6.0	5.8	11.7	12.3	12.3	14.8
	C	20	20	5.8	5.6	11.5	12.1	11.9	14.4
H. E.	R	19–19	21–25	4–7.5	7.5–11	8–15.5	12–19	12–19	12.5–21
	A	19	22.6	6.0	9.0	10.7	15.2	14.9	16.6
	C	20	20	6.3	7.2	11.3	12.2	15.6	14.6
R. M.	R	20–20	18–19	7–11	8–11	13–20	11–21	17–23	15–23
	A	20	18.6	8.4	8.7	16.5	16.8	20.5	19.7
	C	20	20	8.4	9.3	16.5	18.1	20.5	21.1
F. S.	R	21–21	20–20	9–12	5–16	14–21	11–25	19–21	15–27
	A	21	20	10.1	8.2	17.2	18.5	21.6	22.6
	C	20	20	9.6	8.2	16.4	18.5	20.5	22.6
C. M.	R	18–20	18–22	6–7.5	3.8	9–14	7–14	8–15	14–19
	A	19	20.2	6.8	6.1	11.4	11.7	12.6	16.4
	C	20	20	7.1	5.9	12.0	11.3	13.5	16.0

* R = Range of amplitudes in mm.

† = Average of measured amplitudes to nearest 0.5 mm. of 7 consecutive cycles.

‡ = Average amplitude corrected to pendulum deflection of 20 mm. by proportion 20 (Standard pendulum): X (wave to be corrected): : Pendulum deflection measured: Wave deflection measured.

(See table 1.) The correction is allowable, since the actual recorded amplitude of both the pendulum deflection and the ballistocardiographic deflections depends upon the string sensitivity of the recording apparatus, and will retain a constant ratio at different levels of sensitivity (fig. 3). Table 1 illustrates the similarity of amplitudes of the ballistic waves for each of the subjects from one date to another.

2. The second aspect of the study was to check the validity of such calibration as a method of comparison of ballistocardiograph amplitudes from subject to subject. It would seem logical that if the sensitivity of the entire ballistic apparatus, including the body mass and its suspension, the transducer and the recorder be such that a standard external force (pendulum blow) results in a deflection of the same amplitude in different subjects, the internal circulatory forces producing the complexes of the ballistocardiogram should be roughly comparable in those subjects.* If this be true, then from the data assembled by Starr,[8] one would anticipate that the ballisto-

* Such comparison is affected in the present study by the fact that the frequency response curve of the apparatus used is not flat within the range of frequencies recorded. In addition, the augmentation or resistance to circulatory forces by body oscillation distorts this relationship. As improved technics are developed the relationship should be more precise.

cardiograms of young normal subjects would have a relatively narrow range of amplitudes and would be of greater amplitude than ballistocardiograms of subjects with myocardial disease; similarly, ballistocardiograms of subjects with normal cardiovascular systems but in the older age groups would be of only slightly smaller amplitudes than records of young normal subjects. Table 2 shows the amplitude of the IJ wave of the ballistocardiogram of 30 subjects recorded and calibrated as described above. Ten of the subjects were normal medical students and house officers 30 years old, or younger. Ten of the subjects were persons in the age group of 30 to 64 years, with various diagnoses but without any evidence of cardiovascular disease after exhaustive study. Ten of the subjects had definite evidence of heart disease (fig. 4).

Figure 5 is a distribution graph showing the ratio of the IJ amplitude to the pendulum deflection amplitude. Calculated as:

$$\frac{\textit{Pendulum deflection amplitude}}{\textit{IJ amplitude}} = \textit{Ratio.}$$

This is in essence an expression of the percentage relationship between the pendulum deflection and the ballistic deflection. It was adopted for convenience, since it allows division of a smaller number into a larger. The ballistic waves could as readily be expressed as per cent of the pendulum deflection.

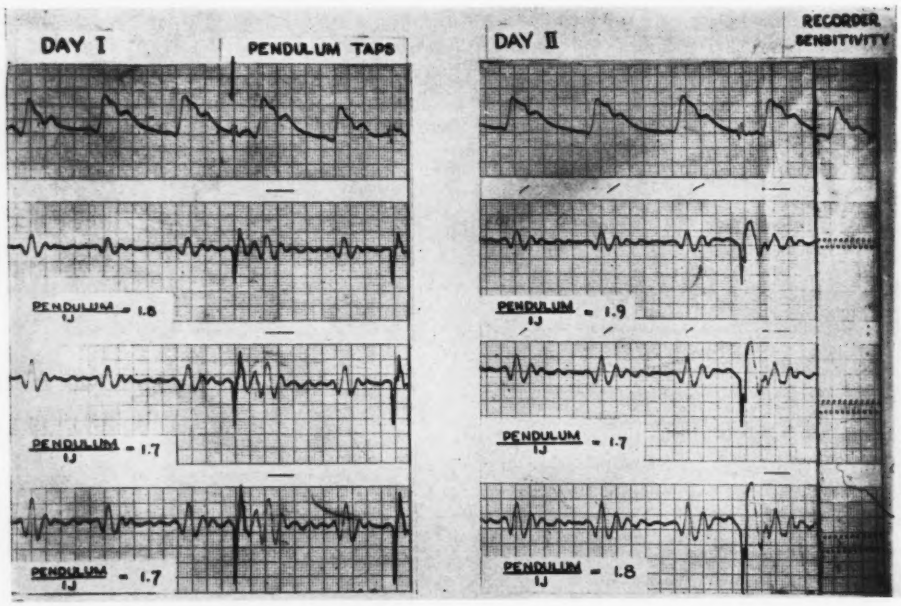

FIG. 3. Subject R. G. T., 24 year old normal male. Records were made on separate occasions. The output of one transducer was recorded on three channels, each with a different string sensitivity. Note that the pendulum deflection amplitude ratio to ballistic deflection amplitude remains constant at different levels of string sensitivity and on separate occasions.

Each of the IJ amplitudes represents the average of the extremes of seven consecutive complexes, measured visually to the nearest 0.5 mm. It will be seen that all of the young normal subjects had ratios within a relatively narrow range from 1.1:1 to 1.8:1, while those subjects with definite cardiovascular disease had ratios from 2.2:1 to 11.4:1; 50 per cent of these subjects had ratios greater than 4:1. The ratios of the normal subjects of the older age groups were all 3:1, or under.

TABLE 2.—*Range of Amplitudes*

Name	Age	Diagnosis	Pendulum Deflection Amplitude in mm.		IJ Amplitude		Pendulum IJ Ratio
			Range	Av. Range	Range	Av. Range	
A. Young Normal Subjects, Studies Made during Quiet Breathing							
J. A. L.	29	Normal	20–20	20	7–15	11	1.8/1
W. D. A.	25	Normal	20–20	20	10–20	15	1.3/1
E. B.	24	Normal	20–22	21	9–15	12	1.7/1
H. E.	25	Normal	19–21	20	7–16	11.5	1.7/1
K. W.	28	Normal	22–23	22.5	10–14.5	12.7	1.7/1
C. McC.	26	Normal	18–22	20	7–14	10.5	1.9/1
R. M.	25	Normal	18–19	18.5	15–21	18	1.1/1
F. S.	28	Normal	21–21	21	14–21	17.5	1.2/1
R. G. T.	24	Normal	20–21	21	10–16	13	1.6/1
T. J. R.	30	Normal	18.20	19	12–20	16	1.1/1
B. Subjects in Older Age Groups with Normal Cardiovascular Systems							
N. R.♂	43	Anxiety	20–20	20	12–16	14	1.3/1
E. McD.♂	53	Anxiety	23–23	23	7–11	9	2.5/1
A. C. Q.♂	41	Chest wall pain	22–24	23	7–15	11	2.0/1
E. N.♂	38	Normal	20–22	21	5–10	7.5	2.8/1
Dr. S.♂	48	Normal	18–18	18	7–10	8.5	2.1/1
P. F. C.♂	59	Normal	19–23	21	6–15	11	1.8/1
M. K.♀	38	Normal, P.V.C.	20–20	20	4–9	6.5	3.0/1
M. D.♂	49	Normal	13–15	14	7–10	8.5	1.6/1
F. D.	51	Normal, chest wall pain	20–20	20	5–8	6.5	3.0/1
T. R. H.	52	Normal	20–20	21	7–14	11	1.8/1
C. Subjects with Abnormal Cardiovascular Systems							
Wh.C.	49	Aortic stenosis	18–18	18	2.5–3.0	2.8	6.5/1
W. P.	73	A.S.H.D. with card. insuffic.	22–24	23	2–11	6.5	3.5/1
W. C. K.	49	A.S.H.D. with old myo. infarct.	20–20	20	8–13	11	2.1/1
J. L. H.	69	A.S.H.D. with old myo. infarct.	18–20	19	4–11	7.5	2.5/1
M. Y.		A.S.H.D. with A.P.	25–26	25.5	2–5	3.5	7.4/1
J. B. G.	50	A.S.H.D. with angina pectoris	22–22	22	1–2.5	1.75	12.6/1
J. H. R.	57	A.S.H.D. with old myo. infarct.	22–22	22	2–9	5.5	4.0/1
W. R.	52	Rh.H.D., M.S., card. insuffic.	15–16	15.5	3–5	4	3.8/1
P. G.	66	Senile H. D., card. insuffic., minimal	23–23	23	4–10	7	3.2/1
M. H.	63	A.S.H.D. with card. insuffic., severe	23–24	23.5	2–5	3.5	6.4/1

P.V.C. = Premature ventricular contractions.
A.S.H.D. = Arteriosclerotic heart disease.
A.P. = Angina pectoris.
Rh.H.D. = Rheumatic heart disease.
M.S. = Mitral stenosis.

DISCUSSION

The data presented above suggest that it is possible, by the use of a standard external force, to overcome the difficulties of transducer adjustment so that quantitative comparison may be made of the ballistocardiograms of a subject made at different times. It will be noted that the maximal deviation of the IJ amplitude of any subject from day I to day II is 11 per cent. This difference is probably a

result of several factors, including slight variations in the timing of the pendulum blow so that the force was augmented or resisted slightly by the oscillation of the body, error in measurement, and slight change in the state of the circulation. One would not anticipate that under the conditions of the test, the circulation would be precisely similar from time to time.

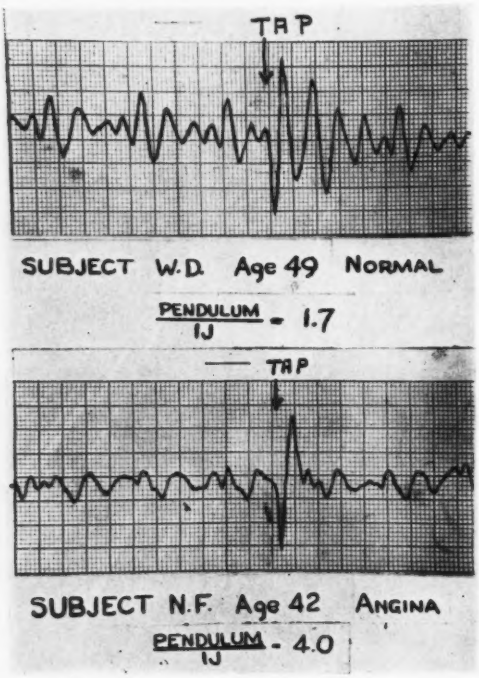

FIG. 4. Ballistocardiograms on subjects in same age group, illustrating the increased pendulum to IJ ratio in cardiovascular disease.

Of greater interest is the result of the comparison of ballistic amplitude in the different subjects. It was somewhat surprising to note the rather narrow range of amplitude in the young normal group, since the weight, height, and body build varied greatly in these subjects. The fact that the subjects with cardiovascular disease had much smaller amplitudes than did the normal subjects of the same age groups would suggest that the principle of comparison of the amplitudes of the ballistocardiograph complexes to the amplitude produced by a standard external force as an index to the circulatory force is valid.

No attempt was made to set up any range or standards of normality from this preliminary study, which is concerned only with testing the validity of a principle. It seems reasonable,

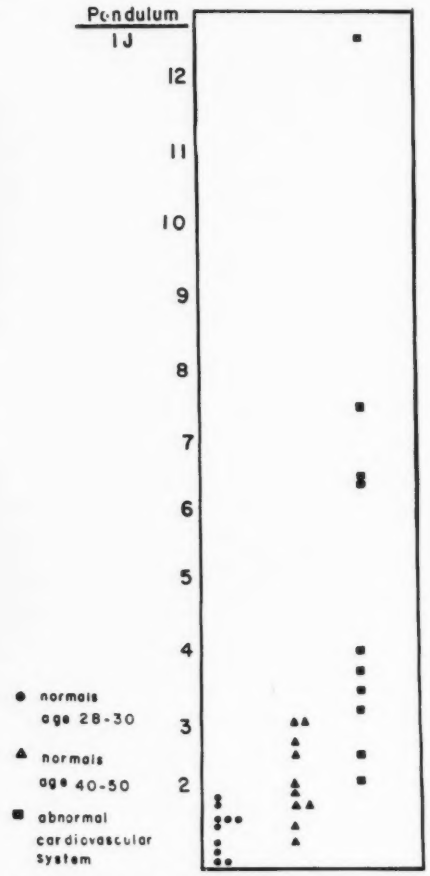

FIG. 5. The distribution of 30 subjects, in regard to pendulum to IJ ratios is illustrated.

however, to assume that from such a method of calibration a general guide to relative ballistic amplitude can be obtained, increasing thereby the value of the direct methods of recording the ballistocardiogram. Any clinician using such technics should check the ratio of pendulum deflection amplitude to ballistic amplitudes on a number of normal subjects with his own apparatus, before attempting to interpret

records from possibly normal subjects. It should be further noted that ballistocardiography is as yet in its infancy, and that the direct method is still in utero. Great caution should be used in clinical application.

Summary

1. A modification of a method by Dock and Taubman for calibration of ballistocardiograms recorded by direct methods is described.

2. Data to support the validity of the method as a means of restoring apparatus sensitivity to a desired level are presented.

3. Data indicating that the use of such technic of calibration allows a quantitative comparison of ballistocardiograms from subject to subject are presented.

Addendum

Although the Dock electromagnetic apparatus was used in recording all tracings reported here, experience with a photoelectric device suggests that the technics described are applicable to it as well. It is reasonable to assume that other transducers would give similiar results.

Sumario Español

Un método simple para calibrar la amplitud del balistocardiograma directo utilizando una fuerza externa al cuerpo standard, se describe. Este método tiende a neutralizar muchos de los variables en la alineación y sensitividad del aparato, y provee una base para la comparación de las amplitudes en el mismo y diferentes sujetos. Normales de grupos de diferentes edades fueron estudiados y el contraste con los anormales con enfermedad cardiovascular conocida se demuestra.

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Correlation of Ballistocardiogram with Work Performance and Energy Cost for Guidance in Rehabilitation of Cardiac Patients

By HENRY BROWN, M.D., SEYMOUR H. RINZLER, M.D., AND JOSEPH G. BENTON, PH.D., M.D.

Correlative studies of the resting ballistocardiogram and the ability to expend energy in cardiac patients indicate that the resting ballistocardiogram may be a useful tool in evaluating the functional or work capacity of a cardiac patient for rehabilitation purposes and vocational guidance, and may serve as a screening device for finding those cardiacs, other things being equal, who possess the functional capacity to perform jobs or activities whose energy requirements are known or can be estimated. However, in view of the relatively higher incidence of abnormal resting ballistocardiograms in the older age groups, for practical purposes, this usefulness of the ballistocardiogram may be limited to the cardiac patient under the age of 50.

WITH the introduction in 1949, by Dock and Taubman,[1] of a simplified electromagnetic device for recording the ballistocardiogram, great impetus was given to the study of clinical ballistocardiography and considerable experience has been accumulated[2-7] which does not differ essentially from that derived from the use of the more complicated instruments of Starr and Nickerson.[8-11]

Significant diagnostic ballistocardiographic changes have been found in patients with coronary artery disease, particularly with angina pectoris. Taymor and associates[4] found that the resting ballistocardiogram was abnormal in 62 (83 per cent) of 75 patients with angina pectoris, normal resting electrocardiograms and positive Master two-step tests. After exercise the ballistocardiogram became abnormal in an additional eight patients, or a total of 70 (93 per cent). Rinzler and co-workers[7] compared the usefulness of the resting ballistocardiogram with the exercise tolerance test in the diagnosis of coronary artery disease in 24 patients with chest pain and normal resting electrocardiograms, and found a 91 per cent correlation; that is, an abnormal resting ballistocardiogram was associated with an abnormal exercise tolerance test, or a normal resting ballistocardiogram with a normal exercise tolerance test, in 91 per cent of instances. The Mandelbaums[5a] reported that 200 of 224 patients with clinical angina pectoris had abnormal resting ballistocardiograms. These findings suggest that the resting ballistocardiogram may serve as a sensitive indicator of coronary artery disease.

Since the ballistocardiogram is a reflection of the mechanical or pumping activity of the heart, it might be expected to give information about cardiac functional capacity. Evidence for this has been presented by Starr[12] who found that patients in congestive heart failure demonstrated abnormal ballistocardiographic patterns, with return to normal patterns upon recovery of cardiac compensation. Starr and Wood[8] also noted good correlation between the ballistocardiogram and *subjective* exercise tolerance as determined by *history* from the patient. The Mandelbaums[5a] found, as a rule, that following a myocardial infarction, those patients whose records approached normal or showed only grade I changes made a better

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functional recovery and were able to return to "full activity."

We have been particularly interested in the problem of rehabilitation of cardiac patients[13, 14, 15] and since definite knowledge of the functional capacity of such patients would be of value in guiding the course of rehabilitation, especially vocationally, the present study was undertaken with the following purposes: (1) to determine if any correlation existed between the ballistocardiogram at rest and the ability of a cardiac patient to do work or expend energy, and (2) if a correlation were found, to decide if it warranted the use of the resting ballistocardiogram as a simple, clinical source of information for guidance in planning rehabilitation programs for cardiac patients.

Methods

This study was conducted during the course of an investigation of the energy cost (in terms of oxygen consumption) of standardized activities in a series of ambulant cardiac patients.* Included in these activities was step-walking on a staircase, which was chosen because it represents an activity requiring no learning or training and one which is essential in the daily life of every individual who is employed outside of his home. Inability to perform this function would place an almost insurmountable barrier in the path of occupational rehabilitation of most cardiac patients.

The patients in this study were drawn from several sources†: (1) Medical wards (Second and Fourth Divisions) of Bellevue Hospital; (2) Fourth Medical Division Cardiac Clinic of Bellevue Hospital; (3) College Cardiac Clinic, New York University College of Medicine, University Hospital; and (4) referrals to the Bellevue Hospital Rehabilitation Service for job placement. The cardiac diagnosis was established in each instance by complete diagnostic examinations on the respective services; many of these patients had been followed in cardiac clinics for a number of years. All of the patients were re-evaluated by us[15] before being included in the present study. None of them had clinically significant skeletomotor disability, or pulmonary, endocrine or hematologic disease.

Patients with all etiologies of heart disease and functional classification I through III were included (table 1).

Table 1.—*Distribution of Cardiac Etiologies and Functional Classifications in 51 Cardiac Patients*

Cardiac Etiology	No.	Functional Classification	No.
Arteriosclerotic	10	Class I	12
Hypertensive with or without arteriosclerosis	12	Class II	23
Rheumatic	17	Class III	18
Syphilitic	2		—
Congenital	2		
Other†	8		
Total	51	Total	53*

* Two patients evaluated at two different times.

† This group includes indeterminate etiology, nonspecific pericarditis, constrictive pericarditis, possible and potential heart disease, and doubtful rheumatic-type heart disease.

As part of the cardiac evaluation, ballistocardiograms were recorded routinely on all patients in the resting state, after lying in bed or on the ballistocardiographic table for at least 10 to 15 minutes. The Dock type electromagnetic instrument was employed in conjunction with a direct writing electrocardiograph, and in most of the records simultaneous QRS complexes (lead I or II) of the electrocardiogram superimposed on the ballistocardiographic tracing were recorded by the method of Gubner[19] for the purpose of observing time relationships.

Many workers in clinical ballistocardiography have reported records taken at rest and after exercise. In the present study, ballistocardiograms were not recorded after exercise for the following reasons: (1) Following completion of the exercise (step-walking) the patient returned to rest in a sitting position and remained connected to the respirometer for another 6 to 10 minutes while recovery phase oxygen consumption was being recorded. This precluded, for technical reasons, the recording of postexercise ballistocardiograms. (2) Experience has indicated that immediately after exercise artefactual distortion of the ballistocardiographic record is very common, probably due to the

* The detailed data and statistical analysis of the investigation of energy costs will be published in the future.

† We are indebted to the following for access to clinical material: E. Hugh Luckey, M.D., Director, 2nd (Cornell) Medical Div., Bellevue Hospital; Charles F. Wilkinson, Jr., M.D., Director, 4th (New York University Post-Graduate) Medical Div., Bellevue Hospital; Charles A. Poindexter, Jr., M.D., Chief, 4th (New York University Post-Graduate) Medical Div. Cardiac Clinic, Bellevue Hospital; Arthur C. DeGraff, M.D., Chief, College Cardiac Clinic, New York University College of Medicine, University Hospital.

increased amplitude and frequency of the respiratory excursions of the thorax and diaphragm. (3) Finally, it was our purpose to determine the usefulness of the resting ballistocardiogram as a simple clinical tool and as a possible replacement for the performance of stress tests in cardiac patients. Therefore, it is to be emphasized that mention of ballistocardiographic records herein indicates those taken in the resting state.

Step-walking was performed on a conventional staircase six steps high with a total height of 42 inches at the rate of six round trips (up and down) per minute (except for one slower test). This rate of work is approximately equivalent to six times the energy cost of the average resting metabolism.[15] The graded activities consisted of the following tests: six trips in one-and-a-half minutes (slow "six-trip"); six trips in one minute ("six-trip" test); nine trips in one-and-a-half minutes ("nine-trip" test); 12 trips in two minutes ("12-trip" test); 18 trips in three minutes ("18-trip" test), and 24 trips in four minutes ("24-trip" test). The "nine-trip" test is approximately equivalent to a standard Master "two-step" test (21 trips) in terms of the rate and the vertical distance through which the subject lifts his own weight.

The step-walking tests were usually performed in the morning during the fasting state or at least two hours after breakfast. Except in those instances where the patient's ability to perform the test was poor, two or three morning sessions on separate days were required to complete the tests. When patients manifested symptoms of angina, dyspnea, or moderate weakness in any test, the series was discontinued at that point, and the most strenuous test completed was designated the maximum work performance of the patient.

During the performance of these tests, the subject was breathing 100 per cent oxygen through a closed system respirometer and oxygen consumption (corrected to normal temperature and pressure) as a measure of the energy cost of the activity was calculated from the respirometric records.[13, 15] Since the work done by each subject varied directly with his weight, the energy cost was calculated in relation to the body weight (milliliters per kilogram).

There were thus available for comparison simultaneous data of the patient's ability to do work of graded intensities, the energy cost, and the resting ballistocardiogram. These data were examined for the existence of any correlation between the normality of the ballistocardiogram and the amount of work that the patient could perform. To maintain objectivity, the ballistocardiograms were analyzed and interpreted without original reference to the patient's energy expenditure or maximum work performance.

Interpretation of Ballistocardiograms

Since the ballistocardiograms recorded by the Dock type instruments do not allow critical quantitative measurements, interpretation depends on a qualitative study of the ballistic forms or wave patterns. The unquestionably normal ballistocardiogram can easily be identified. The pattern is regular and repetitive and the H, I, J, and K waves are sharply defined and easily identified. Where the pattern is so grossly distorted and bizarre that the wave forms are indistinguishable, abnormality is obvious. There are, however, patterns of fairly regular and repetitive complexes which many believe are also abnormal.[2, 4, 5, 7, 8, 16, 17, 18] These include (1) an H wave amplitude equal to or taller than the J wave; (2) marked diminution in amplitude or absence of the I wave; (3) late notching or double-peaking of the J wave; (4) an excessively deep (and often late) K wave associated with a relatively small HIJ complex; (5) an absent K wave.

It should be noted that such qualitative terms as "marked diminution in amplitude" and "excessively deep" are used in describing criteria of abnormality, and this allows for certain differences of opinion in interpretation and the designation of "borderline" tracings. It is hoped that this shortcoming of a method which is at present qualitative rather than quantitative, will be obviated with further refinement of the ballistocardiographic technic.

Although most of the ballistocardiograms in the present series were recorded in various phases of respiration, it was noted that the best tracings were obtained with respiration held at the end of a normal expiration. Other investigators[5b, 16] have attached great significance to the variations occurring with the phases of respiration, but during this study similar variations in many normal persons were observed and it is believed that the present state of knowledge does not allow any particular significance with respect to cardiac function to be attributed to the respiratory variations.

Results

Fifty-one cardiac patients were studied for a total of 53 tests (two patients were studied

at two different times) and a summary of the results is given in table 2. The data are tabulated to indicate the maximum work performance, the mean energy cost in terms of oxygen consumption (milliliters per kilogram of body weight in excess of resting at normal temperature and pressure) for each category of work and their correlation with the resting ballistocardiogram.

TABLE 2.—*Comparison of the Resting Ballistocardiogram with the Maximum Work Performance and Mean Energy Cost of Each Category of Work Performance in 53 Cardiac Patients*

A*	B†	BCG Interpretation			
		Normal	Abnormal	Borderline	Indeterminate
Slow "6-trip"	22.7	0	5	0	0
"6-trip"	21.5	0	1	0	0
"9-trip"	30.7	3	10	0	0
"12-trip"	40.0	3	3	1	0
"18-trip"	57.0	7	3	1	4
"24-trip"	72.5	11	1	0	0
Totals		24	23	2	4

* Column A indicates the various categories of maximum work performance. Maximum work was determined by a series of step-walking tests of increasing energy costs continued to the point of first manifestation of symptoms.

† Column B gives the mean energy cost for each category of work performance in terms of oxygen consumption (milliliters per kilogram of body weight, at standard temperature and pressure, dry) in excess of resting metabolism.

In 24 patients, normal resting ballistocardiograms were obtained and all of these subjects were able to complete the "nine-trip" test, the performance of which resulted in a mean energy cost of 30.7 ml. per kilogram; this is nine times the resting metabolism for one minute (3.39 ml. per kilogram per minute for 50 cardiac patients in this study). Eighteen of these patients (75 per cent of those with normal ballistocardiograms) were able to do the "18-trip" test, or better, with a mean energy cost of 57.0 ml. per kilogram, or greater, an increase of at least 16.8 times above the requirements for one minute of resting.

Of 23 patients with abnormal resting ballistocardiograms, five could not complete the regular "six-trip" test (mean energy cost of 21.5 ml. per kilogram) and only four (17.4 per cent of those with abnormal resting ballistocardiograms) were able to do the "18-trip" test, or better, with a mean energy cost of 57.0 ml. per kilogram.

Two patients with borderline tracings were able to do the "12-trip" and "18-trip" tests, respectively. In four patients the ballistocardiogram was considered as indeterminate. These tracings were taken early in the course of the study before simultaneous electrocardiograms were recorded and there was some question about the identity of segments of the complexes. All four completed the "18-trip" test (mean energy cost of 57.0 ml. per kilogram).

The chi-square test for homogeneity was applied to the data, excluding borderline and indeterminate cases, and chi-square was found to be highly significant, with p, the probability if chance alone were operating, less than 1 in 1000.*

When the data were grouped in a two-way classification, they showed that 21 out of 24 in the group with normal and only 7 out of 23 in the group with abnormal ballistocardiograms had a work performance of over nine trips. The difference between these two proportions was tested statistically and was found to be highly significant with p for chi-square less than 1 in 1000.

Discussion

The results indicate that a normal resting ballistocardiogram in a known cardiac patient is associated with the ability to perform work of a moderate to marked increment in energy cost (from 9 to 16.8 times, or greater), above the resting level during a relatively short period of time.†

The significance of this lies in the fact that very few working activities other than heavy

* We are indebted to Dr. Donald A. Mainland, Professor of Biostatistics, Department of Preventive Medicine, New York University College of Medicine, for review of the statistical data.

† Unpublished data from this laboratory indicate that in a group of about 50 normal persons, in general, the mean energy expenditure for the performance of the identical tests is not significantly different from the values herein reported for the cardiac patients.

manual labor require a sustained output of more than two to four times the resting energy expenditure. It has been pointed out[20] that work may be considered moderate when its cost is three times that of the basal rate and strenuous when the cost increases to eight times the basal rate. Therefore, it may be postulated that these patients have a good to excellent potentiality for work of moderate energy costs, other factors being equal. On the other hand, according to the data in this study, an abnormal resting ballistocardiogram is *not* prognostic of the patients' work performance, for such patients fell into all categories of maximum work performance and energy cost from the least to the greatest.

the usefulness of the ballistocardiogram, namely, that the value of the resting ballistocardiogram for the determination of work potentiality may be greatest in cardiacs under the age of 50 years. Such information can still be of great assistance with regard to rehabilitation and vocational guidance for the large population of patients with rheumatic cardiac disease, as well as those with coronary artery disease in the fourth to fifth decades.

The data with reference to functional classification offer additional support for the usefulness of the ballistocardiogram. Clinical experience with cardiac patients indicates that the assignment of a specific functional classification is often conditioned by the physician's own

TABLE 3.—*Comparison of 24 Cardiac Patients with Normal Resting Ballistocardiograms and 23 Cardiac Patients with Abnormal Resting Ballistocardiograms According to Age, Etiology of Heart Disease, and Functional Classification*

Subjects	Etiology of Heart Disease						Functional Class*			Age	
	As	Hyper ♂ or ♀ As	Rheum	Syphilitic	Cong	Other	I	II	III	Mean Yrs.	Range Yrs.
With Normal BCG	5	3	9	1	2	4	11	8	5	37.0	16-58
With Abnormal BCG	6	6	6	1	0	4	0	12	11	50.5	32-67

* Where available, the functional class was obtained from the cardiac clinic record of the patient; otherwise it was determined by us after evaluation of the history and physical examination of the patient.

A comparison of the 24 patients with normal resting ballistocardiograms, and the 23 patients with abnormal resting ballistocardiograms, reveals a similar distribution of the various cardiac disease etiologies in each group (table 3). However, it also reveals a significant difference in the mean ages of the two groups; namely, 37.0 years for the "normals" and 50.5 years for the "abnormals." It has been demonstrated that the incidence of abnormal ballistocardiograms increases with each decade of advancing age,[9, 21] and there seems to be little doubt that extracardiac factors related to aging are important in producing many of the abnormalities of the ballistocardiogram in older persons. However, this age difference would not seem to invalidate the present conclusions, since in no case was a normal resting ballistocardiogram (six were found in patients over 45 years of age) associated with a poor work potentiality, but it does suggest a practical limitation to

fears and prejudices about the patient's ability to do work, to say nothing of the latter's anxieties and exaggeration of symptoms. The frequency with which disabling cardiac neurosis (superimposed on nondisabling organic disease) is met in the cardiac clinic is proof enough of this and is one of the greatest obstacles to the rehabilitation of the cardiac patient. What is sorely needed is an objective means of functional classification and the present data indicate that the resting ballistocardiogram may offer assistance in this regard. In table 3, it can be seen that 16 patients were assigned the functional classification III, on the basis of history, physical examination and the usual cardiac laboratory data, by competent cardiologists. This means that these 16 patients were considered to be relatively severely disabled, since, according to the criteria of the New York Heart Association,[22] class III patients are defined as those who are comfortable at rest,

but have discomfort in the form of undue fatigue, palpitation, dyspnea or anginal pain caused by less than ordinary activity. Actually, the present studies demonstrated that in work performance, 12 of them were able to perform the "nine-trip" test, or better, with a mean energy cost of 30.7 ml. per kilogram, or greater. In five of these patients (two completed the "18-trip" test, two the "12-trip" test, and one the "nine-trip" test), the resting ballistocardiogram was normal. It is evident that the ballistocardiogram is a better indicator of work performance (functional capacity) than the history and physical examination in at least 5 of the 12 patients.

Such considerations have bearing on our particular interest in the problem of the rehabilitation of cardiac patients, and it may be seen that these preliminary findings have special significance, for they suggest that the resting ballistocardiogram may be a useful tool in evaluating the functional or work capacity of a cardiac patient without subjection to a series of tests calculated to "titrate" work capacity. In this connection, it should be noted that there are those[23, 24] who feel that exercise tests carry with them an attendant hazard. The present findings also indicate that the resting ballistocardiogram may be used as a screening device for finding those cardiac patients who have the functional capacity to perform certain jobs whose energy requirements are known or can be estimated by physical demands analysis, and in whom the extremely important factors of motivation and other psychologic considerations are not a barrier to useful employment.

It is of special interest that in the series of 24 patients with normal resting ballistocardiograms there are five who had sustained one or more myocardial infarctions and all were able to complete the "18-trip" or "24-trip" tests, activities with a high energy cost. All were placed in selected jobs and are now working full time supporting their families.

Summary

1. In 51 known cardiac patients of all etiologies and functional classification I through III, a comparison was made of the resting ballistocardiogram and the ability to do work and expend energy as determined by a series of step-walking tests of graded intensities, while oxygen consumption was measured in a closed system respirometer.

2. The results indicate that under the conditions studied, a normal resting ballistocardiogram in a known cardiac patient is very frequently associated with the capacity for moderate to marked energy expenditure. An abnormal resting ballistocardiogram gives no consistent information about the patient's work capacity. Statistical analysis of these correlations is highly significant.

3. Furthermore, the resting ballistocardiogram, *when normal*, appears to be a more accurate indicator of the functional classification of a cardiac patient than the assignment of a classification on the basis of the interpretation of the cardiac history and physical examination.

4. This suggests that the resting ballistocardiogram (a) may be a useful tool in evaluating the functional or work capacity of a cardiac patient for rehabilitation purposes and vocational guidance, and (b) may serve as a screening device for finding those cardiacs, other things being equal, who possess the functional capacity to perform jobs or activities whose energy requirements are known or can be estimated. However, in view of the relatively higher incidence of abnormal resting ballistocardiograms in persons in the older age groups, for practical purposes this usefulness of the ballistocardiogram may be limited to the cardiac patient under the age of 50 years.

Addendum

In a recent study and review which appeared while the present paper was in press, W. R. Scarborough and co-workers (Am. Heart J. **44:** 645, 910, 1952) indicate a limitation to the usefulness of the ballistocardiogram in diagnosing coronary artery disease in patients over the age of 50 years, which is similar to the limitation we found in its usefulness for evaluating functional capacity.

Acknowledgment

We are indebted to Vilma Smith, B.A., for technical assistance.

Sumario Español

Estudios correlativos del balistocardiograma en reposo y la habilidad de usar energía en pacientes cardíacos indica que el balistocardiograma en reposo puede ser un instrumento provechoso en la evaluación funcional o de capacidad de trabajo de un paciente cardíaco para propósitos de rehabilitación y guía vocacional, y además puede servir para encubrir cardíacos que poseen la capacidad funcional de trabajar en oficios o participar en actividades cuyas demandas de energía ya se saben o se pueden estimar. Sinembargo, en vista de la incidencia relativamente alta de balistocardiogramas en reposo anormales en el grupo de edad avanzada, el uso provechoso de balistocardiograma para propósitos prácticos se debe limitar a pacientes cardíacos de menos de 50 años de edad.

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CLINICAL CONFERENCES

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Rheumatic Mitral Insufficiency

By HOWARD B. BURCHELL, M.D., AND JESSE E. EDWARDS, M.D.

THE case on which the present clinicopathologic conference is based involves a 33 year old woman with rheumatic heart disease. The salient points in the history are as follows: At the age of 12 the patient was ill for a year with what was diagnosed rheumatic fever, and at the age of 15 she was ill for three months with this same condition. At the age of 18 she underwent a pregnancy which was unassociated with any recognized disability. At the age of 22 (1941), five days before the delivery of her second child, the patient had pain in the thorax and required treatment with an oxygen tent. She gave birth to a living child but was advised not to become pregnant again.

Symptoms of cardiac disability began at the age of 26 (1945) at the time of an upper respiratory infection which was associated with much dyspnea, cough and the spitting up of small amounts of blood. At this time digitalis therapy was begun. A year later the patient was told that her heart action was irregular, and this irregularity had persisted to the present time (1952). In 1948 she had an induced abortion with ligation of the fallopian tubes. Since that time she had remained ill with epigastric distress which at first was noted with exercise and relieved with rest. In the last two years it had been present more or less constantly. This distress had been temporarily relieved by the injection of mercurical diuretics. During the past year there had been some orthopnea and two episodes of severe nocturnal dyspnea. In the same period she had had slight edema of the ankles and had been hospitalized frequently.

Of possible interest is the fact that in February 1951, following dental extraction, there was rather marked weakness and recurrent sweats. No blood cultures were taken, but the doctor told her that he suspected infection of the heart valves, and she was given penicillin every two hours for five days, followed, evidently, by no persistence of fever.

When she was admitted to the hospital on June 2, 1952, under the care of the Mayo Clinic, her weight was 103 pounds (46.7 Kg.) and her blood pressure 120/70. She was in moderate distress because of dyspnea. The liver was readily palpable and tender and it extended to the umbilicus. Clinically the heart was greatly enlarged, and at the apex a systolic murmur of grade 2 intensity and a middiastolic rumble were noted. The thoracic roentgenogram showed marked enlargement of the heart which seemed to include all the chambers, and there was good evidence of left atrial enlargement (fig. 1*a*). The problem arose whether the patient had mitral stenosis or mitral insufficiency as the predominant lesion. After careful consideration it was believed justifiable to recommend surgical exploration with the thought that the basic problem might be one of mitral stenosis. Though considered an unfavorable situation, exploration seemed indicated. At operation a high degree of mitral insufficiency was found to be present. The patient's postoperative course was "stormy" and she died seven days after operation on June 30, 1952.

From the Division of Medicine and the Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

COMMENT

The exposure by the surgeon of the physician's incompetence in diagnosing mitral incompetence (insufficiency) has, in this era of mitral surgery, been more acutely embarrassing to, and less easily forgotten by, the physician than the occasional errors of diagnosis previously pointed out by pathologists. In the scramble to re-entrench themselves the internists have critically examined the traditional and the newer laboratory signs which have been the factors on which a presumptive diagnosis of stenosis or insufficiency or both has been based, and have found them less satisfactory than they had been wont to believe. Some of the problems that are undergoing critical analysis in probably every medical center concern re-evaluation of the significance of the apical systolic murmur, enlargement of the heart generally and of the left atrium and of the left ventricle in particular, studies of the pulsation of the left atrium, the presence of valvular calcification, the electrocardiographic picture, and measurements of left atrial pressures taken either directly, or

indirectly as by the wedging of the cardiac catheter into a pulmonary artery.

It may be pointed out that the person with a small heart and a very typical loud diastolic rumble at the apex *has* mitral stenosis, and with this diagnostic sign there has been no conflict.

In accord with the plan of this pathologic conference, the various problems which this patient brought up may be listed in terms of questions intended primarily to highlight the features in the clinical differential diagnosis between mitral stenosis and mitral insufficiency.

How may the apical systolic murmur be evaluated as an indication of the presence of mitral insufficiency?

In general, the louder the apical systolic murmur that is heard the more likely it is that the patient has mitral insufficiency. This generalization has greater validity if the systolic murmur is well heard in the axilla and there is no diastolic murmur. However, there are exceptions, and we have seen patients who have had tight mitral stenosis without insufficiency as determined by the surgeon and who had had only a loud (grade 2 to 3) apical systolic murmur. A rare patient with mitral stenosis may have evanescent murmurs and even mimic, at first examination, an idiopathic pulmonary hypertension. It may be pointed out that it has been our teaching for some years that an apical systolic murmur of moderate intensity consequent to, and related to, mitral rheumatic valvulitis is not necessarily indicative of mitral insufficiency. The organic background of such a murmur has been attributed to a distortion of the outflow tract of the left ventricle caused by scarring and distortion of the anterior leaflet.

What is the significance of the size of the heart and of the left atrium as evidence of mitral stenosis or insufficiency?

When the right ventricle is greatly enlarged it may form the apex of the heart, and it is most difficult if not impossible for the roentgenoscopist to recognize with certainty an associated left ventricular enlargement. While characteristically patients with mitral stenosis have smaller hearts than those with mitral insufficiency, there are exceptions.

Enlargement of the left atrium has been properly taught to indicate mitral stenosis, but the enlargement may be just as great in patients with mitral insufficiency. A possible exception to this may be the few tremendous aneurysmal dilatations of the left atrium that have been recorded with mitral stenosis. Also it may be noted that some patients whose mitral stenosis is demonstrable pathologically may have only slight enlargement of the left atrium. It may be emphasized, however, that the left atrium at postmortem examination may not appear large, but if the heart is left intact and the atrium distended with pressure equal to that which may be present during life there is a much better appreciation of its large size.

Is the size of the left ventricle as judged roentgenologically of help in distinguishing mitral stenosis from mitral insufficiency?

The size of the left ventricle is an important feature in considering the differential diagnosis of these two conditions. If the left ventricle shows signs of enlargement and there is not concomitant involvement of the aortic valve or acute rheumatic myocarditis, the diagnosis of mitral insufficiency is favored. In the case being presented the radiologic and electrocardiographic evidence supported the presence of both right and left ventricular enlargement (fig. 1*b*).

What is the significance of calcifications of the valve?

This patient had an easily recognized area of calcification which was associated with the mitral valve disease (fig. 1*a*). Clinically we have associated calcification with a stenotic orifice, both in disease of the mitral valve and in disease of the aortic valve, but again the relationship is not one of reliable diagnostic import. A calcified lesion usually indicates that the orifice of the valve is narrower than normal, but the stenosis may not be of functional significance. Rather, an associated

mitral insufficiency may be the paramount lesion from a functional point of view.

Of what significance is the increased angle between the main bronchi, viewed roentgenologically, in the diagnosis of left atrial enlargement?

This is a well-recognized roentgenologic sign associated with enlargement of the left atrium, but it is of minor importance. Incidentally the elevation of the left bronchus is believed to play a role, along with the pulmonary artery, in the production of paralysis of the left recurrent nerve which is experienced by some patients with disease of the mitral valve. This patient did not, however, have evidence of such paralysis. The major extents to which the left main bronchus may be angulated and to which its intrinsic shape may be deformed may not be generally appreciated but can be demonstrated very graphically in tomograms.

What is the possibility of a previous subacute bacterial endocarditis causing valvular destruction and mitral insufficiency?

It is generally known that in bacterial endocarditis minimal lesions of the mitral valve, rather than tight stenosis, are encountered. A corollary of this is that patients with rheumatic mitral disease and auricular fibrillation rarely have subacute bacterial endocarditis. In the case under discussion clinical evaluation had to take note of the previous episode of a febrile illness for which penicillin was administered, since the occurrence of mitral insuf-

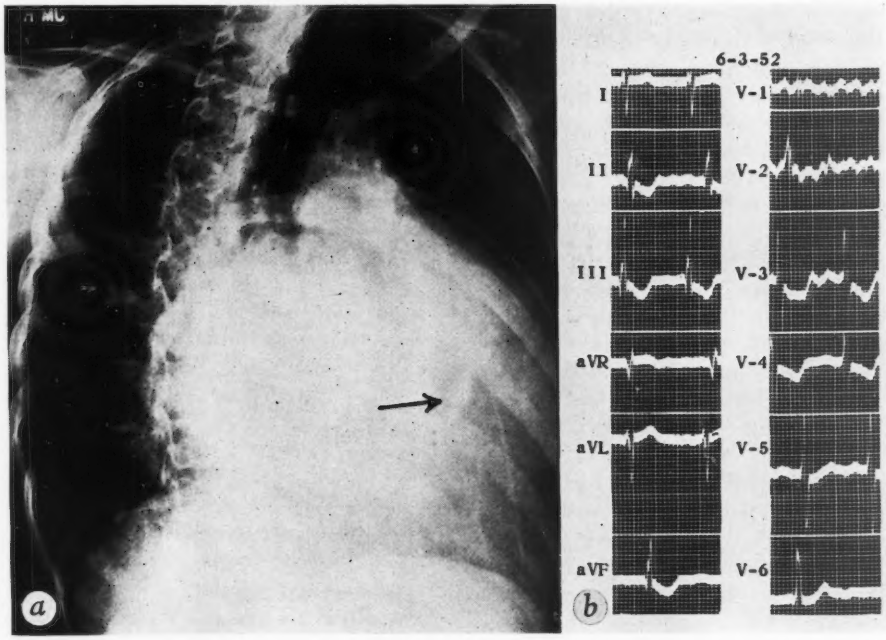

FIG. 1*a*. Roentgenogram of the thorax taken in the right anterior oblique position showing the marked enlargement of the heart, particularly the left atrium and right ventricular outflow region, and calcification of the mitral valve (point of arrow).

b. Electrocardiogram showing auricular fibrillation and right axis deviation. The high notched R wave in V_2 and the R deflection with the slight delay in the intrinsicoid deflection in V_5 were interpreted as indicating hypertrophy of both right and left ventricles.

ficiency as a manifestation of healed bacterial endocarditis had to be borne in mind.

How reliable is the electrocardiogram in differentiating mitral stenosis and mitral insufficiency?

It is apparent that in the usual case the electrocardiogram should be of great value, and this has been supported in general by our experience with cases of mitral disease in which surgical treatment has been given. With few exceptions, in the cases in which operation for mitral stenosis has confirmed the condition, the experience of our group has been that right ventricular hypertrophy was indicated in the electrocardiogram by right axis deviation and a high R wave in lead V_1 or aV_R. However, in cases in which there is mitral insufficiency, the pattern of left ventricular hypertrophy may be expected, but we have observed exceptions in which the evidence of marked right ventricular hypertrophy dominated the electrocardiographic picture. In the case discussed here the electrocardiogram could be best interpreted as indicating both right and left ventricular hypertrophy (fig. 1*b*).

Of what value is cardiac catheterization in the differential diagnosis?

(The catheterization findings in this case are given in table 1.)

Correlative studies of cardiac catheterization data seem to indicate that pressures in the pulmonary artery are apt to be somewhat lower and the cardiac output less fixed in cases of mitral insufficiency than in cases of mitral stenosis in which there is the same degree of cardiac failure. Such trends, if they exist, cannot be relied upon in evaluating an individual case. The wedge pressure contours for the individual patient, however, may give some clue as to the presence of mitral insufficiency as opposed to mitral stenosis, but again these are not wholly dependable. Connolly and co-workers[1] have found that wedge pressures at the time of operation are practically equal in magnitude and contour to the simultaneously recorded left atrial pressure. In addition even a direct left atrial pressure record may not be diagnostic of an existing mitral insufficiency which the surgeon is able to demonstrate. These observations have caused us to doubt that esophageal pressure records will differentiate with uniform success mitral insufficiency from mitral stenosis.

The data obtained on cardiac catheterization in the patient under discussion are compatible with either mitral stenosis or insufficiency but cannot be considered to favor one condition over the other.

TABLE 1.—*Catheterization Findings**

Site	Pressure, mm. Hg		Oxygen saturation, %
	Maximum	Minimum	
Right atrium	12	8	49
Right ventricle	84	9	53
Pulmonary artery	95	53	49
Pulmonary artery (onset of exercise)	160	65	—
Right ventricle (4 minutes after exercise)	115	15	27
Radial artery	129	84	96

Cardiac index: rest, 1.34 liters per minute per square meter; exercise, 1.73 liters per minute per square meter.

Wedge pressure not obtained.

* Courtesy of Dr. E. H. Wood.

Of what value are special procedures designed to register the amplitude of the left atrial pulsations?

The problem here is mainly whether the moderately incompetent orifice of the valve might cause the marked systolic pulsation of the left atrium that may sometimes be seen on roentgenoscopy in the presence of very gross incompetency; from evidence gained at the time of operation it would seem doubtful that such pulsations would be discernible with moderate incompetency. With the special procedures of electrokymography and roentgenkymography we have had no experience.

If pulmonary biopsy were feasible, would it be possible from a study of the pulmonary arteries and arterioles to differentiate mitral stenosis and insufficiency?

Becker and we[2] have already published evidence that mitral insufficiency may be

associated with severe obstructive lesions of the small arteries and arterioles identical with those seen in mitral stenosis; hence, even this hypothetic test would be unreliable. It may also be mentioned that the degree of severity of vascular lesions seen in biopsy sections of the lung has not correlated well with the hemodynamic data obtained by cardiac catheterization or with the clinical improvement following surgical treatment.[3]

What did the surgeon find on exploration of the heart?

The surgeon (Dr. John W. Kirklin) noted at thoracotomy that the heart was immense, that it was pushed forward by a very large left atrium, that it probably was the largest left atrium he had seen, and that an expansile systolic pulsation of slight degree could, it seemed, be recognized in it. No thrill was palpable. The pulmonary artery was greatly enlarged and tense. Even before the heart was entered it was thought that the condition was mitral insufficiency; when the valve was explored digitally there was a very forceful turbulent flow coming back through the valve during ventricular systole. Regurgitation seemed to be coming mainly from the site of the medial commissure, and here the posterior leaflet seemed to be greatly deformed and heavily scarred. There was a question of slight stenosis of the mitral valve, since the lateral commissure was elongated by fusion of the leaflets, but further opening of the valve was thought not to be indicated.

What was found at necropsy?

The heart was enlarged, weighing 525 Gm. Most striking was the dilatation of the left atrium which contained about 400 cc. of blood. The left ventricle was moderately dilated and hypertrophied (fig. 2*a*). The right ventricle was moderately hypertrophied. The condition of the mitral valve was classified pathologically as a combination of rheumatic stenosis and insufficiency, although the degree of stenosis was relatively small, the mitral orifice measuring about 2.5 cm. in diameter. The existing narrowing of the orifice was brought about almost exclusively by changes at the anterolateral commissure (fig. 2*a* to *c*). Here there was marked fusion of the two leaflets which in this region were thickened with considerable calcified material. Thus there was good confirmation of the surgeon's appraisal of the lesion.

The anterolateral mitral commissure was elongated while the posteromedial commissure was of normal depth. The chordae tendineae universally were moderately thickened, with relatively minor degrees of shortening. There was little evidence of fusion of chordae except immediately beneath the anterolateral commissure. The anterior leaflet, except for thickening by calcified material at its boundary with the anterolateral commissure, was only slightly thickened and its length was normal. The posterior leaflet was uniformly thickened by fibrous tissue to a moderate degree except at its lateral extremity where it shared with the anterior leaflet the process of marked thickening and calcification. Neither of the mitral leaflets showed any defects which could have been interpreted as evidence of healed bacterial endocarditis.

In the region of the posterior leaflet the ring of the mitral valve was dislocated, lying superior to the epicardial aspect of the left ventricular myocardium. Whereas normally the long axis of the endocardium of the left atrium in this region is in essentially the same plane as the endocardium of the underlying left ventricle (fig. 2*d*), in this case the lower portion of the posterior wall of the left atrium assumed a horizontal position (fig. 2*e*). This portion of the endocardial surface of the left atrium was at right angles to the endocardial surface of the underlying left ventricle. The altered position of the wall of the left atrium caused the lower part of this chamber to assume a position immediately above the basilar myocardium of the left ventricle. It is suggested that the short posterior leaflet of the mitral valve and the posterior dislocation of the valve ring were results of tension upon the ring and leaflet by the dilated left atrium.

Structural evidence for the existence of mitral insufficiency was to be had in the impossibility of closing the mitral orifice when attempts were made to bring the two leaflets

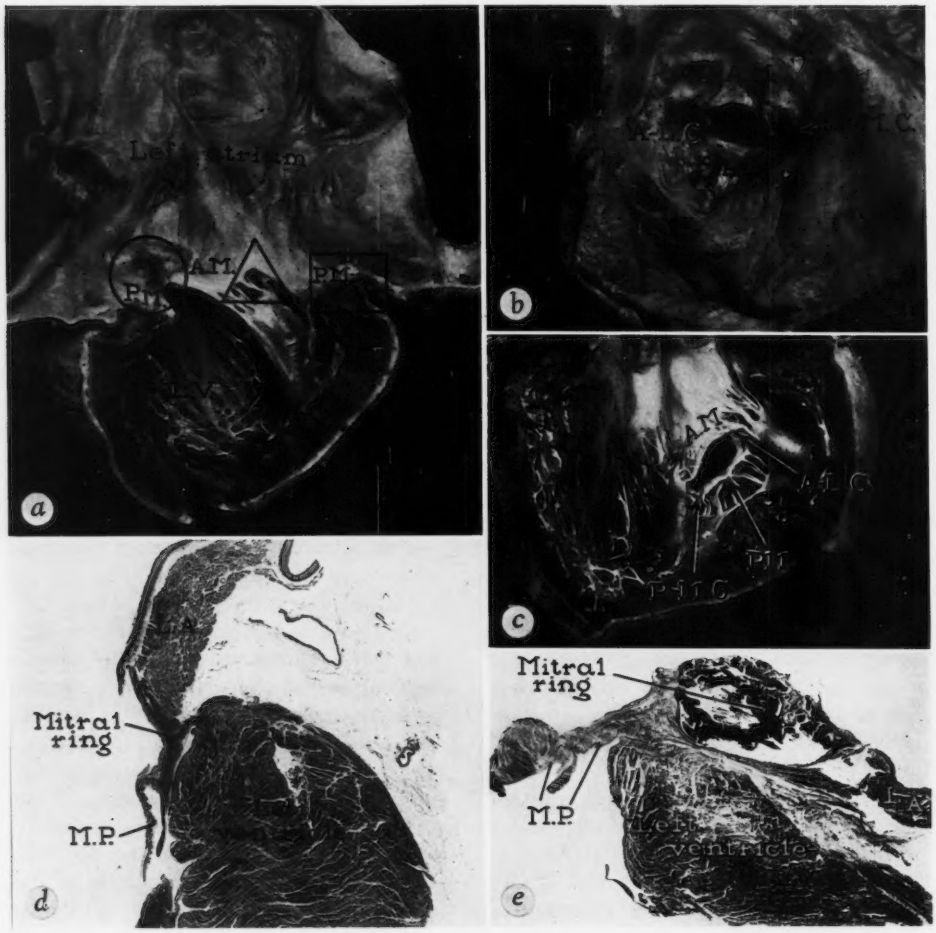

FIG. 2*a*. Left side of the heart. The left atrium is greatly dilated. The left ventricle is moderately dilated and hypertrophied. There is fusion of the anterior (*A.M.*) and posterior (*P.M.*) mitral leaflets at the anterolateral commissure (circle) with calcification. The posteromedial commissure (triangle) is essentially normal. The posterior leaflet is shortened and retracted. The endocardial surface of the lower portion of the left atrium above the posterior leaflet of the mitral valve is at right angles to the endocardial surface of the left ventricle. In this region the epicardial surface of the left atrium bulges beyond that of the left ventricle. The area shown in the rectangle is illustrated as a photomicrograph in *e*. (Similar abbreviations are used in the other parts of the figure.)

b. The mitral valve from the left atrial aspect. The anterolateral commissure (*A.L.C.*) is deeper than normal because of fusion of the anterior and posterior mitral leaflets. Calcification is present in this region. The posteromedial commissure (*P.M.C.*) is essentially normal. The mitral orifice is wide.

c. The mitral valve from the left ventricular aspect. The mitral orifice is gaping, and the posterior leaflet is short. The chordal changes are relatively mild.

d. A longitudinal section through the posterior leaflet of the mitral valve and adjacent left atrium and ventricle of a *normal heart*. The endocardial surface of the left atrium in this region is in essentially the same plane as the endocardial surface of the left ventricle. The mitral ring lies over the endocardial portion of the left ventricle.

e. Section similar to that illustrated in *d* but from the case presented. The section is taken from the area outlined by the rectangle in *a*. The left atrial endocardial surface is at right angles to the left ventricular endocardial surface, and the epicardial portion of the left atrium is displaced outward. The mitral ring, which is calcified, is dislocated posteriorly, lying above the epicardial half of the ventricular myocardium and its overlying epicardium. The posterior mitral leaflet (*M.P.*) is thickened and shortened.

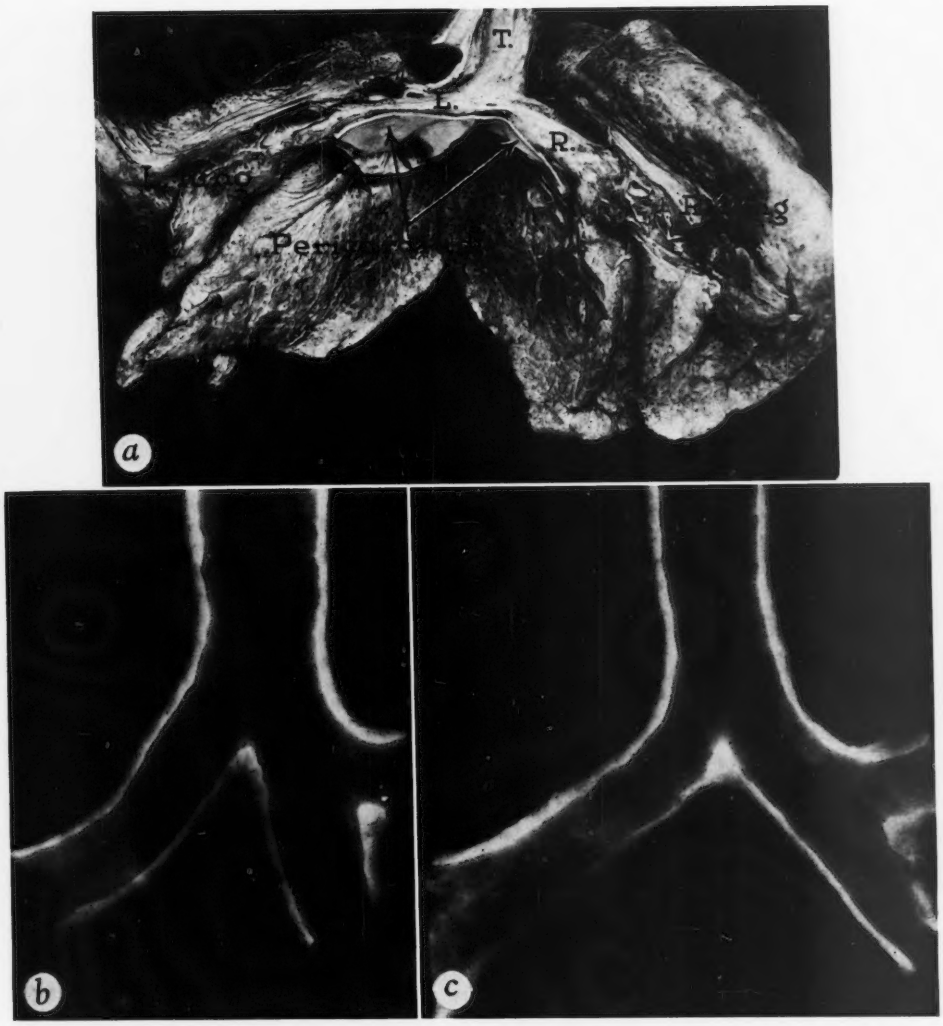

FIG. 3*a*. The tracheobronchial tree and lungs from behind. The angle between the left and right bronchi is increased. The left main bronchus (*L.*) is flattened, giving the posterior aspect of this structure a sharp rather than a rounded character. The changes shown have resulted from pressure by the dilated left atrium. The parietal pericardium overlying the left atrium has been left in place and in contact with the tracheal bifurcation. *T.* signifies trachea; *R.* right main bronchus.

b. Roentgenogram of a normal tracheal bifurcation, viewed from behind, for comparison with *c*.

c. Roentgenogram of the tracheal bifurcation, viewed from behind, in the case presented. The angle between the two major bronchi is about 90 degrees (the normal is about 50 degrees). This results principally from upward dislocation of the left main bronchus (*L.*), a consequence of its having been displaced upward by the dilated left atrium.

in apposition. Supportive evidence was had from focal thickening in the posterior wall of the left atrium which appeared to represent reactions to the trauma of regurgitant blood.

There were interesting alterations in the tracheobronchial tree where it was associated with the underlying dilated left atrium. One of these was an increase in the angle between the right and left bronchi as they arose from the trachea (fig. 3*a* to *c*). It appeared that the

greatest factor leading to this increase in angle was displacement upward of the left main bronchus by the enlarged left atrium.

In addition to the deviation of the left main bronchus from its normal direction, there was further evidence of compression of this structure: the opposing faces of the left bronchus were virtually in apposition along one aspect of the structure. The posterior aspect of this bronchus had a sharp edge instead of being rounded (fig. 3*a*), and there was a change in cross sectional contour (fig. 4).

Elsewhere in the heart, there was slight thickening and shortening of the leaflets of the aortic valve. The pulmonary valve was normal. The leaflets of the tricuspid valve were slightly thickened but were not fused or shortened. The foramen ovale was closed anatomically. The venous connections to the heart were normal. The ductus arteriosus was closed. The coronary arteries were essentially normal.

Grossly, the lungs were uniform and slightly reduced in crepitation. The cut surface presented a uniform moist appearance and exuded moderate amounts of blood-stained frothy fluid.

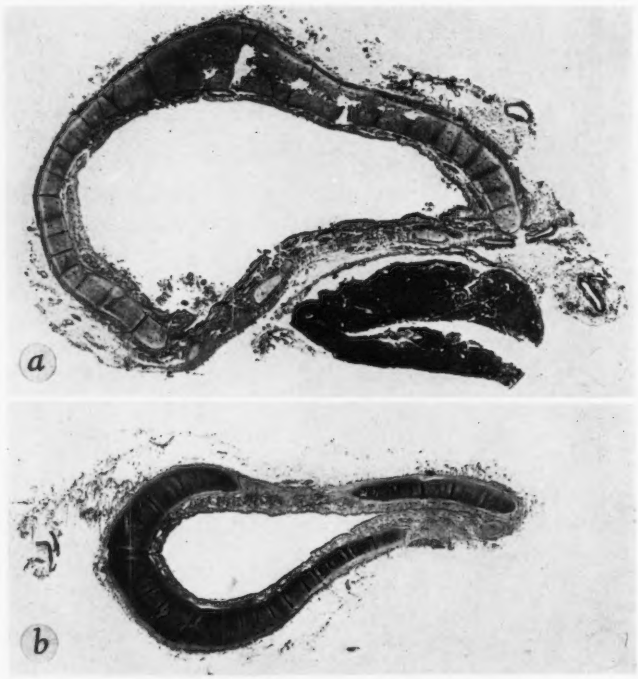

FIG. 4*a*. Cross section of a normal left main bronchus (hematoxylin and eosin; ×6).

b. Cross section of the left main bronchus from case being presented. At the right side of the illustration, which corresponds to the posterior aspect of the bronchus, the superior and inferior walls have been pressed into close apposition, a consequence of the existing dilatation of the left atrium during life. The cross sectional contour is quite different from that of the normal left main bronchus illustrated in *a* (hematoxylin and eosin; ×6).

Microscopic examination of the lungs revealed features similar to those seen in cases in which the lesion is that of mitral stenosis. The lungs were characterized in part by increase in thickness of the alveolar walls by the presence of relatively thick bundles of collagen. In places there were lining cells having cuboidal characteristics. The alveolar spaces, in foci, contained moderate to considerable numbers of macrophages laden with hemosiderin. In the pulmonary vascular system there was

moderate medial hypertrophy of small and medium-sized muscular arteries. The arterioles showed varying, at times severe, degrees of intimal fibrous thickening. Often this fibrous tissue was laid down in a concentric manner. The venules showed changes similar to those in the arterioles. The walls of the small veins were thickened by muscular hypertrophy and increase in density of connective tissue elements of the media. In addition there were varying degrees of intimal fibrous thickening in this class of vessel.

From a pathologic point of view the mitral valvular lesion in this case is to be classified as that of stenosis and insufficiency. The degree of stenosis, however, was relatively minor in that the orifice measured about 2.5 cm. in diameter and probably, for this reason, constituted no significant barrier to ventricular filling. It is to be emphasized that this size of mitral orifice is far greater than that obtained after adequate mitral valvulotomy in cases of predominant mitral stenosis. The mitral insufficiency appears to have been the cause of the cardiac disability.

It is frequently taught that when mitral stenosis is present there is always some degree of mitral insufficiency. While such a statement may be true if the slightest amount of regurgitation is to be considered "insufficiency," the surgeon has now established that mitral stenosis is often a pure lesion unassociated with recognizable insufficiency. Further support of the concept that mitral stenosis frequently exists as a pure lesion is the correlation that is found between the calculated areas of the mitral valve, according to the method of Gorlin and Gorlin,[4] and the surgeon's appraisal of the orifice of the valve.

What is the pathogenesis of chronic rheumatic mitral insufficiency?

Of particular interest is the deformity of the posterior wall of the left atrium observed in this case as in other cases of pronounced dilatation of the left atrium. There is intimate connection between the endocardium of the left atrium and the posterior leaflet of the mitral valve. It appears reasonable, therefore, that dilatation of the left atrium would cause traction on the posterior leaflet of the mitral valve and cause it to be pulled away from the mitral orifice. That this had happened in the case presented is suspected by the fact that the mitral ring was farther posterior than it is normally. To what degree a dilated left atrium might contribute to the initial stages of mitral insufficiency is difficult to determine. It is possible that a chain of events operated as follows: Primarily, shrinkage of the posterior leaflet as a result of rheumatic endocarditis could have initiated a degree of mitral insufficiency. Resulting dilatation of the left atrium would in turn have been followed by retraction posteriorly of the entire leaflet, except where it was fused to the anterior leaflet at the anterolateral commissure, and accentuation of the mitral insufficiency. In this way it is possible that a vicious circle was set up in which mitral insufficiency caused left atrial dilatation and left atrial dilatation further increased the degree of mitral insufficiency.

At this point it might be asked whether, if this reasoning is correct, the dilated left atrium causes mitral insufficiency in cases of predominant mitral stenosis. To this question a negative answer is applicable. With fusion of the two leaflets at both commissures it would appear that the effect of the dilated left atrium upon the posterior leaflet would be to distort the entire mitral valve and to cause the position, but not the size, of the orifice to be changed. It will be recalled that in the case presented there was considerable fusion at the anterolateral commissure. There was little, if any, appreciable fusion between the leaflets at the posteromedial commissure. This would allow the posterior leaflet to be displaced posteriorly by an enlarged left atrium.

Are the bronchial deformities described in this case unique?

The deformity of the tracheal bifurcation, particularly with reference to the position of the left main bronchus and the change in cross sectional contour of the left bronchus, is a feature which has been observed by us in other cases of left atrial dilatation as part of a study in progress. The change in contour of the cross

section of the left main bronchus in this circumstance would seem to cause a degree of stenosis of that structure. The narrowing of the left bronchus in the case presented could conceivably have been overcome by removal of the underlying cause, namely, dilatation of the left atrium. It is also possible, however, that were bronchial ulceration for any reason to have occurred, the healing process could have caused fusion of opposing walls of the bronchus with resulting organic and permanent bronchostenosis.

Given a heart with stenotic changes in the mitral valve, can the pathologist say with certainty that insufficiency was or was not evident to the surgeon who had had an examining finger in the left atrium?

In the usual instance with significant mitral insufficiency the pathologist may readily demonstrate inadequacy of the valve leaflets to close the orifice. He may also demonstrate regurgitant "jet lesions" in the endocardium of the left atrium. There is an occasional case, however, in which, to the pathologist, the problem seems to be essentially one of mitral stenosis while at operation the surgeon had clearly felt the regurgitant flow through the mitral orifice.

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CLINICAL PROGRESS

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Coarctation of the Aorta

By ROBERT E. GROSS, M.D.

CONSTRICTIONS can occur anywhere in the aorta from the midpoint of the arch down to the bifurcation of the vessel. A few are found in the abdomen or in the lower thorax, but fully 98 per cent of them are located in the first part of the descending aorta, just beyond the arch.

PROGNOSIS

Since most children and young adults with coarctation of the aorta do not have symptoms, there is a rather widespread belief that the malformation is an innocuous affair. The fact that a few humans with aortic narrowing have lived to advanced old age has given a false impression that the prognosis is generally not serious. There is now increasing evidence to show that coarctation leads to crippling complications or even fatality in a very large percentage of cases.

A study of the prognosis for humans with coarctation has indicated[21] that about one fourth of them have lived through a rather long life with little or no incapacitation, that about one fourth have died of rupture of the aorta, that one fourth have died from superimposed bacterial endarteritis, and one fourth have died from the hypertensive state. In the last group, death occurred either from cardiac failure or from intracranial hemorrhage.

As one summarizes available material regarding the prognosis for patients with coarctation, several general statements can be made. The average age at death (including persons who have died from coarctation or one of its complications) has been about 30 years. It has become quite clear that, while some subjects may live a long and useful life with coarctation, the abnormality is one which generally brings great hazards to its possessor. It is this knowledge which prompts surgeons to attempt removal of aortic obstructions in the hope of bettering the outlook, particularly in alleviation of the hypertensive state.

From the Surgical Services of the Children's Hospital and the Peter Bent Brigham Hospital, Boston, Mass.

CLINICAL PICTURE

Sex

Coarctation is about twice as common in males as in females.

Ease of Recognition

With but rare exceptions, coarctation of the aorta can be detected quickly by finding a few signs which are evident on physical examination. In these days, when there is an increasing tendency to employ expensive and complicated laboratory tests, it is appropriate to point out that coarctation can be diagnosed accurately in a few moments by the intelligent use of one's finger tips, a stethoscope, and a sphygmomanometer.

Differences in Pulsation

Of greatest importance in detecting an aortic obstruction is the disparity between pulsations (or blood pressures) in the arms and legs. Beats in the legs or lower part of the body are diminished or absent. If femoral pulsations appear to be reduced in intensity, the pressures in the popliteal artery should be checked with a sphygmomanometer. Normally, the systolic level in the legs is 20 to 40 mm. Hg higher than that in the arms; in the presence of an aortic block the leg pressures are far below those in the upper part of the body.

Under normal circumstances, the impulses in the femoral and radial arteries come almost at the same instant. In the presence of coarctation, the femoral artery beat starts at a slightly later time and there is a slow rise of the wave. These lags can be recognized easily by simultaneous palpation of the radial and femoral arteries.

Hypertension

In young subjects with coarctation, pressures in an arm may be normal or only slightly elevated, whereas in older persons one commonly finds hypertension of moderate or marked degree. Certainly, in the majority of patients beyond the second decade, hypertension is the rule. The systolic pressure may be greatly elevated; in advanced cases, the diastolic level can be raised 10 to 30 mm., or more.

Hypertension Varies with Activity. Blood pressure determinations made during an office visit or when a patient is at rest in bed do not indicate the state of affairs when he is undertaking exercise or is undergoing the physical strain of daily life. The value observed during rest is usually distinctly lower than that which occurs during routine activity. It is well known that a normal person reacts to exercise by slight or moderate elevation of blood pressure. In contrast, a patient with coarctation generally responds by an extraordinary rise. The increased demands of the body raise the cardiac output, but the large quantity of blood ejected from the heart meets an obstructed vascular tree; hence, there is a momentary and steep upward swing of pressure in the head and arms.

Pressure Measurements in Both Arms. Arterial pressures should be measured in both arms because this might give a clue to detection of those constrictions which lie in the arch itself. Differences of 10, 20, or even 30 mm. Hg between the two arms can be found in individuals who are normal and also in those who have an obstruction beyond the origin of the left subclavian artery. Conversely, a pressure which is more than 30 or 40 mm. Hg lower in the left arm than in the right suggests that the aorta is narrowed in a place proximal to the origin of the left subclavian artery, an item of great significance when discussing the feasibility of surgery.

It is well to bear in mind that large differences in arm pressures can also be caused by atresia (or hypoplasia) of the first part of the left subclavian artery, a finding in several of our patients. Furthermore, Stephens described a subject in whom the right subclavian artery did not originate from the innominate, but instead arose from the aorta below the obstruction; the arterial pressure in the right arm was distinctly lower than that in the left.

Accessory Arterial Channels

Collateral arterial circulation is by no means constantly observed, but when found it strongly favors the diagnosis of coarctation. By physical examination, it is rarely seen in children, but beyond the first decade it becomes evident both by inspection and palpation. Pulsations may be seen and felt above and below the clavicles, in the axillae, along the intercostal spaces in the forward half of the chest, in the epigastrium, and particularly over the upper half of the back. When collateral circulation is marked, pulsations sometimes appear in the anterior abdominal wall and can be traced downward to the inguinal regions.

Murmurs

There is nothing characteristic about the murmurs which are found; they are extremely variable in form, in intensity, and in location. A few subjects with coarctation have no murmur; a small number have continuous ones. Most often, but by no means constantly, there is a systolic murmur of mild or moderate intensity over the precordium, especially toward the base, which is transmitted with slight diminution to the left side of the interscapular area. In some instances, the murmur is louder in the back than it is in the front of the chest. Murmurs over the back do not, by their point of maximum loudness, give an indication of the actual level of the aortic anomaly.

We have little in the way of accurate information regarding sources of murmurs which

appear in patients with coarctation. It is tempting to think that blood passing through a narrowed aortic segment sets up the vibration, but there is ample proof that this is not always true. While a systolic murmur in some instances is known to come from the constricted area, in others it almost certainly originates from an angulated collateral channel, an associated septal defect, a bicuspid aortic valve, or other structural change.

Particular attention must be paid to a diastolic murmur. If it is continuous with the systolic element and is loudest in the pulmonary area, it suggests the presence of a patent ductus arteriosus. If a continuous murmur is most prominent over the back, it may be indicative of blood rushing through large and tortuous collateral arteries. If a diastolic murmur is heard in the aortic area or to the left of the sternum, one should strongly suspect aortic valve stenosis and insufficiency. Slight regurgitations may not produce a depression in the diastolic pressure, but marked reflux is accompanied by a definite lowering. While such disturbances in the aortic valve may have a rheumatic background, commonly they are on the basis of a congenitally bicuspid structure of the valve leaflets.

Cardiac Failure

There is little need to comment on the picture of cardiac failure in adults, which is so common and which can follow long-standing hypertension. Myocardial weakness is one of the outstanding causes of death in patients with coarctation. In childhood, failure is rare but it does occur.

It is well to call attention to a small group of babies who have cardiac embarrassment because of an aortic block. Presumably, these youngsters remain in fair health as long as a ductus arteriosus stays patent and blood can flow from the engorged upper portion of the aorta back into the pulmonary bed. When the ductus closes and this relief mechanism is lost, the left ventricle must pump into a vascular system which has a very high resistance because it is almost devoid of collateral channels. We have seen a dozen babies within the first year of life who had marked cardiac enlargement, dyspnea, cough, enlarged liver, and other signs of a failing heart, such decompensation being secondary to hypertension from an aortic block. Two of these infants died of failure, but the others could be tided over (by hospitalization, oxygen therapy, digitalization, and other medical measures) until they regained cardiac compensation. During this precarious interval of one or two months, they probably developed collateral pathways which allowed an easier outflow of blood and which permitted the heart to regain stability.

Neurologic Deficit

Profound neurologic damage, or even fatality, can occur as a result of intracranial hemorrhage. There may be hemiplegia, or widespread and bizarre neurologic findings, depending upon the position and extent of bleeding within the central nervous system. Such disaster can occur from rupture of a normal vessel which is subjected to increased pressure; not infrequently it comes from a congenital aneurysm in the circle of Willis, rupture being particularly prone to take place when such an anomaly is subjected to the hypertension of a coarctation.

Fainting, dizziness, momentary loss of consciousness or even convulsions can also be seen as a result of hypertensive crises, there being no hemorrhage within the brain.

Ballistocardiographic Findings

The diagnosis of coarctation of the aorta can apparently be made from ballistocardiographic tracings; there is a shortening of the J-K stroke. While this phenomenon is an interesting observation, such investigation is not necessary for routine study.

Electrocardiographic Findings

Electrocardiographic tracings are an important part of the examination, not because they help in recognition of a coarctation, but because they might give evidence regarding the presence of some other co-existing cardiovascular anomaly. Furthermore, electrocardiograms can indicate whether hypertension has inflicted any damage upon the myocardium.

In children the electrocardiogram is apt to be normal, but in older subjects a left-axis deviation is the rule. In patients beyond 20 to 30 years of age, patterns of serious left ventricular strain or bundle branch block are ominous findings when discussing the possibility of operative removal of a coarctation.

Roentgenographic Findings

By roentgenographic study there may be certain findings in childhood to help support the diagnosis of coarctation; in adult years the changes usually become more pronounced and clearly indicate the presence of this abnormality.

In infancy one seldom finds more than generalized cardiac enlargement unless, in the rare case, there happens to be additional evidence of circulatory failure. During the first 8 or 10 years of life there may be little variation from normal except possibly for some left ventricular prominence and some diminution in the size of the aortic knob. In and beyond the teens, the roentgenologic findings are more numerous and more conclusive; the heart generally shows mild or moderate increase in size, particularly of the left ventricle. Great enlargements should arouse suspicion regarding the possibility of some concomitant abnormality, myocarditis, coexisting rheumatic disease, or cardiac failure. The base of the ascending aorta is apt to be widened. The left subclavian artery is usually seen to be enlarged; it results in a prominence of the left side of the superior mediastinum. The aortic knob or distal part of the aortic arch is smaller than normal. Though it is by no means a constant finding, the descending aorta appears indented if the patient can be turned to an angle which will separate this shadow from the spine. In many cases, it is impossible to see the constriction of the aorta.

Scalloping of the inferior edges of the posterolateral portions of ribs is pathognomonic of an aortic block with development of collateral circulation. Such erosion is seldom found in the upper or the lower two or three ribs. It rarely appears before 8 or 10 years of age; it is generally present in teen-agers, and it is almost always apparent in adult patients.

Of unusual occurrence is the situation described by Bing and his associates[3] in which the left subclavian artery arose from the aorta below its block; there were collateral channels on the left side of the chest, the rib notchings were confined to the right side. In this same category is the case of Stephens in which the right subclavian artery arose from the aorta below the obstruction; the rib notches were found only on the left side of the chest. We have seen a similar roentgenologic picture on a different basis in a 12 year old girl in whom the first portion of the left subclavian artery was atretic; chest films showed rib notches which were distinctly more marked on the right than on the left.

Though relatively rare, coarctation may appear in the lower portion of the thorax, or even in the abdominal aorta. Under these circumstances, the aortic knob is normal in appearance and the collateral channels are largest over the abdomen and lower part of the chest; notches appear only on the lowest ribs.

With barium in the esophagus, some irregularity is usually found on its left side, the so-called "E-sign." This esophageal compression can come from that part of the aorta which is dilated just beyond the obstruction, and also from right intercostal arteries which cross the mediastinum to enter the distal aorta. Of great importance to the surgeon is a lateral view of the esophagus; prominent serrations on the posterior aspect of the esophagus indicate the presence of very large right intercostal arteries which course to and enter the aorta below its obstruction. These thin-walled vessels are extremely hazardous to deal with surgically; the roentgenographic picture can forewarn the surgeon of their presence.

Angiocardiogram. Further information regarding the exact position of a stricture, the length of the narrowed segment, and allied data, are obtainable by means of angiocardiography. The radio-opaque material can be injected either by the intravenous route or in a retroarterial manner. Seventy per cent Diodrast, if infused quickly into a vein, will often remain in sufficient concentration through the circulation so that the aortic arch and its

branches can be seen in serial films. All too often, the dye becomes diluted and does not show the great arteries very well. An alternative technic is that in which visualization is obtained by introducing a polyethylene catheter into an artery of the left arm, threading it back through the left subclavian artery into the aorta, at which time the injection is made. Burford and Carson[8] and more recently Freeman and co-workers[10] have obtained excellent pictures of the vessels by injecting Diodrast down a neck artery, preferably the left common carotid, while temporarily obstructing the vessel above the site of injection.

On many occasions I have been disappointed or have been misled by angiocardiography in the study of patients with coarctation of the aorta. At times the dye would show the upper end of the narrowed area, but did not give information regarding the length of the stricture. In other cases, where there was a complete aortic block, nothing was learned about the segment of aorta below it. Presumably, angiocardiography should be of assistance in deciding which cases are suitable for surgery and which are not, but often this is not so. This has been especially true in older patients when visualization might show an arrangement of vessels suggesting that removal of the constricted area would be feasible; when the chest has been opened the vessels were found to be very rigid or fixed and surgical attack had to be abandoned.

Angiocardiography is not an essential part of a routine work-up, but it can be of value in those cases where there are unusual or inexplicable findings. Its greatest usefulness is in those patients who have, by physical examination, an aortic block but who do not have an E-sign on the esophagus and do not have notching of the ribs; they might have either a coarctation or a hypoplasia of the entire aorta. Under these puzzling circumstances, visualization of the aorta generally can settle the differential point.

Selection of Cases for Surgery

Surgery Generally Advisable

It is our belief that almost all patients with coarctation should be operated upon at some appropriate time, provided there are no serious contraindications. Statistics now show that the mortality rates of operation can be kept reasonably low. It therefore seems best to accept these risks, which are almost certainly lower than those of letting the patient go along without therapy. In an occasional case, it might be wise to defer surgery if the blood pressure is in relatively safe levels. However, it is well to remember that, while a child or a young adult may show only slightly elevated pressures, important hypertension is very apt to appear subsequently in later years.

Contraindications

Because certain co-existing conditions have been found to increase enormously the operative risks, there are several contraindications to operation. Rheumatic mitral disease of marked degree, aortic valve regurgitation of serious extent (diastolic murmur of more than grade 3 intensity, or appreciably lowered diastolic pressure), conduction bundle defects (by electrocardiogram), or advanced myocardial damage (by clinical picture or electrocardiogram) are generally contraindications to surgical attack on a coarctation.

Many persons with coarctation have a congenitally bicuspid aortic valve; by itself, this is not a contraindication to surgery. Likewise, a mild degree of insufficiency at such a valve (grade 1 to 3 diastolic murmur, with no important depression of the diastolic pressure) does not seriously increase the risks of surgery.

Optimum Time for Surgery

The optimum ages for operation lie between 10 and 20 years. In this range the aorta is large enough to work upon with facility, has good elasticity, has little or no degenerative change, and provides the best conditions for making an anastomosis which is sizable and satisfactory. The lumen will be large enough to carry the patient through adult life.

Beyond the second decade, patients begin to present situations which greatly increase the difficulties of operation. The heart has less reserve, the chest is larger, the exposure is more difficult, the aorta is more inelastic, and

aneurysms are more frequently encountered in the distal aortic segment or in one of its intercostal arteries. These and other factors make the operative procedures more troublesome for the surgeon and also less promising for the patient. The various difficulties are more apt to be encountered in men; in contrast, women almost always have vessels which are softer, more elastic, and easier to work upon.

Therapy for Babies. Sometimes babies, in the first year of life, have impressive symptoms indicative of cardiac impairment from a coarctation of the aorta; in a few there is fatality. If these patients get beyond the first year, they are then apt to go through childhood without too much difficulty. This poses the question of whether or not an infant who is having cardiac symptoms, should be operated upon. It has generally been our policy to advise against operation at this early age because it appears that the vast majority of these small subjects can be tided over their period of embarrassment by medical means, after which they do reasonably well; we believe that the best chances for a satisfactory operation will come later, between 8 and 12 years of age. We have steered away from surgery in the infant because, while it is technically possible to work upon the aorta and give it a lumen satisfactory for this size patient, there is little assurance that the growth of the anastomotic site will keep pace with that of the individual. From laboratory observations on aortic unions in growing pigs, several investigators have found that it is possible for the lumen to enlarge reasonably well with the increase in size of the maturing animal, but in some instances it lags somewhat behind. Hence, in a human baby, we generally prefer to carry along on temporizing treatment by medical means, and then perform operation later in childhood when there is a more reasonable promise that the pathway will be large enough to be adequate during adult life. That it is possible to treat coarctation surgically in an infant has been shown by Kirklin and associates.[18] Therefore, if medical therapy does not seem to be sufficient to control cardiac failure in a baby, surgery can be undertaken as the indications require.

Operation in Midadult Life. There is no definite upper age limit, beyond which it is advisable to avoid surgical removal of a coarctation. However, after the ages of 30 or 35, surgery should not be undertaken unless it is reasonably certain that the myocardium is in good enough condition to stand the strain of a long major operation, a point which can be best judged by the patient's tolerance for exercise and by the electrocardiographic tracings.

Surgical Therapy

Sympathectomy

We do not believe that sympathectomy is of any value in the treatment of hypertension which is based on coarctation.

Bypass with the Left Subclavian Artery

Blalock and Park[4] suggested a form of treatment for coarctation by severing the left subclavian artery high in the chest and turning it downward for union with the aorta beyond the obstruction. In the presence of coarctation, the subclavian is often of very large size; indeed it may approach the diameter of the aortic arch. This suggests that it would provide an excellent pathway if joined to the distal aorta. There are two drawbacks to such an undertaking: (1) The severance of a subclavian artery cuts off many collateral channels, the loss of which is not inconsequential. (2) The base of a subclavian artery is sometimes semirigid, so that attempts to turn the vessel downward result in a kinking which greatly reduces the effective size of its lumen. While the subclavian operations have given a few good results in relief of hypertension, on the whole they are very disappointing; we have abandoned them completely.

Excision of Coarctation. Primary Anastomosis

The ideal method of therapy—feasible in most instances—is excision of a coarctation and reconstruction of the pathway by bringing together the remaining ends of the aortic tube. Without discussing the minutiae of surgical technic, certain points and general principles are well worth stressing here:

Preparation for Transfusion. Blood loss is

apt to be high in these operations. The chest wall is always exceedingly vascular; in spite of the fact that a very large number of vessels are clamped and ligated, bleeding is considerable. It is necessary to prepare ahead of time for infusion of blood during operation to compensate for this. For children, at least 1000 cc. of blood should be matched before operation; for large children or adults 2000 to 3000, or preferably 4000 cc. should be on hand.

Exposure. To give one's self the best chance to work on the aorta, a generous exposure is of considerable help. There are some surgeons who have employed only an incision in the fourth intercostal space or through the bed of the fourth or fifth rib (after removing the same subperiosteally); we believe these to be inadequate, or certainly they are not optimum. A T-shaped wound in the bony cage gives an ideal view; we use it routinely in all cases. The fourth intercostal space is cut along its entire length, with posterior severance of two ribs above this and two below (in large subjects three ribs are always cut below).

Safest Progression in Liberating Aorta. In mobilizing the aorta and related vessels, it is a very sound principle to *avoid* at first those regions which are apt to be dangerous or difficult to deal with; it is better to begin with the easier parts of the regional dissection. In this way, as one approaches the most risky areas (the upper intercostals, the coarctation, the ligamentum arteriosum), any injury or bleeding can be cared for quickly because the vessels have already been freed and can be handled as needed. Conversely, if one had attacked the most vulnerable parts first and set up a hemorrhage, it is almost impossible to deal with the catastrophe.

With the above thoughts in mind, it is good procedure to start work by freeing up the entire left subclavian artery, carrying this down to include somewhat the anterior and posterior surfaces of the distal arch. Then attention is turned to the aorta *below* the upper two or three sets of intercostal arteries. Down at this low site, it is not difficult or dangerous to circumvent the aorta and get a tape around it. From here the dissection can be carried cautiously upward around and underneath the aorta, dividing any bronchial arteries which are encountered. By tapes, the aorta can be pulled up slightly into the field and away from the vertebral column, which dislocation will aid in identifying and stretching out the upper thin intercostal arteries which are now freed. The coarctation area, the ligamentum arteriosum, and the undersurface of the aortic arch are cleared last.

Saving Intercostal Arteries. To get all of a coarctation cut out, and in addition have enough cuff for making an anastomosis, it is sometimes necessary to divide intercostals which are nearby. In the vast majority of cases these thin vessels are far enough away from the coarctation so that they can be raised from their beds and can be temporarily compressed by small serrefine clamps without hampering too much the subsequent stages of operation; in this way a maximum amount of collateral circulation is spared. It is important to emphasize that it is pointless to save intercostals if doing so compromises the making of a good aortic pathway; the primary objective should be to make a first-rate union of full aortic size, even though some collaterals might have to be sacrificed in attaining this.

Removal of Sufficient Aortic Tissue. It is a fundamental truism that if surgical therapy is going to be successful in the relief of hypertension, it is essential to remove *all* of the coarctation. In the tense atmosphere of operation, it is quite tempting for the surgeon to cut away only the more narrowed part of the constricted zone; he may be fearful that more radical excision will lead to difficulties in approximation of remaining aortic ends. Such a compromise is very apt to be followed by incomplete relief of hypertension. To obtain the best possible results, every effort must be made to remove *all* of the constriction and to establish a pathway which is fully the diameter of the aortic arch.

Form of Anastomosis. In bringing remaining ends of aorta together, it is wrong to attempt an anatomic repair of intima to intima, media to media, and adventitia to adventitia. Though this has been advised and used by some surgeons, it is a distinctly inferior type of union

and it will often give way and disrupt. Overwhelming evidence[14] indicates that the best repair is that in which mattress stitches are taken through the entire thickness of the aortic wall, bringing intima to intima, and turning outward the ends of the vessel. We routinely make the stitches interrupted. The best suture material is 00000 Deknatel silk, carried on a straight needle 5/8 inch long.

Position of Coarctation. The position of a coarctation has much to do with the ease or the difficulty with which it can be excised. Obviously, the surgeon's troubles are least when the block lies well beyond the arch and there is a segment of descending aorta (above the block) which can be comfortably clamped. Unfortunately, many obstructions are at a very high level—just beyond the origin of the left subclavian artery—and indeed they may actually be in the distal part of the arch itself. With high constrictions, the surgeon's problems are tremendously increased, particularly when dealing with older subjects in whom the vessels are rigid. While high blocks should be approached with more caution and apprehension, they do not necessarily present insuperable obstacles. To obtain a proximal stump it may be necessary to place a clamp directly across the aortic arch and across the left subclavian artery so that the latter is partially or totally occluded temporarily.

Excision of Coarctation. Insertion of Graft

Extensive laboratory work[16] (on dogs) has shown that it is possible to transfer an aortic segment from one animal to another (of the same species) and to have it serve as an excellent pathway. Such grafts have been implanted in recipient animals and observed for periods as long as three years. The risk of dilatation, rupture, or thrombosis appears to be negligible. Grafts do show extensive histologic changes, particularly in the media, yet they have a smooth lining and they carry blood in a highly satisfactory manner. While observations from animal work do not necessarily indicate what will happen if aortic segments are transferred from one human to another, there seems to be sufficient experimental background to justify the use of grafts in human subjects to bridge aortic gaps which cannot be treated by any other means.

Aortic segments can be collected from human subjects, preferably young individuals within four to six hours after death. They can be stored in several ways: (1) If gathered aseptically, they can be stored in a modified Tyrode's fluid at 3 to 4 C., and can be used at anytime up to five or six weeks.[16, 17] (2) Sterile segments can be packaged in cellophane bags, frozen in carbon-dioxide ice at −50 or −55 C., and then kept at this temperature for many months. (3) If segments are contaminated during removal from a body they can be frozen, and then sterilized by high-voltage Cathode-Ray irradiation[20]; the sterilized frozen segments can be kept many months and still be useful as grafts. We have used the first method for 29 human subjects, the second for three, and the third for five. We have preferred to use the first method if appropriate material is available. We employ the second method only when there is not available material preserved by the first one. We have used the third method only in those instances when we have no segments which have been stored by the first two methods.

There are certain situations wherein it is impossible to perform the ideal operation of excision of a coarctation and primary anastomosis of the remaining aortic ends: (1) The constriction may be a very long one (several centimeters or more). (2) There may be a very rigid and inelastic aorta which cannot be stretched to overcome even a short gap. (3) There may be an aneurysm in the aorta below the constriction. These various problems are best handled by removing all of the pathologic tissue, cutting back to lumen of full size above, and then inserting a graft.

The need for grafting is only seldom met in childhood. It is required more often for adult patients, where complicated pathology and technical difficulties are more frequently encountered.

Anticoagulants

It is not necessary to administer dicoumarin or heparin to prevent local thrombosis. If the aortic intima is not damaged, and if a

proper anastomosis has been made, the danger of regional thrombosis is negligible.

Analgesia for Wound

The extensive posterior chest wound can give a great deal of pain in the postoperative period. It is of considerable help to the patient's comfort to inject, while the chest is still open, 4 to 5 cc. of Nupercaine in oil around each of the upper six or seven intercostal nerves, infiltrating this material between the necks of the ribs. This provides an analgesia to the chest wall for about a week.

Chest Drainage

Because of the extensiveness of the wound, some serosanguinous fluid always accumulates in the chest after operation. It is therefore best to provide intercostal drainage by a tube for three to four days after operation.

Results of Therapy

Mortality Rates

The surgical treatment of coarctation has been placed on a reasonable basis, carrying low fatality rates. To date, we have operated upon 270 patients; in the first 100 of these there were 15 fatalities, in the last 100 there have been but two deaths. This improvement is ascribed to: (1) Avoidance of operation in subjects who are known to have complicated cardiovascular conditions (noted above under Selection of Cases for Surgery). (2) Abandonment of cyclopropane anesthesia. (3) Attainment of sufficient experience with the operation to give greater facility in handling the emergencies which are sometimes encountered.

Exploratory Operation

In some patients it has been impossible to remove an aortic obstruction because: (1) The patient was tolerating anesthesia poorly. (2) The obstruction was too high in the arch. (3) The vessels were densely adherent to surrounding structures and could not be mobilized. (4) The area of constriction was a very long one, prohibiting excision and primary aortic anastomosis. For these various reasons, attempt at surgical removal of the aortic block had to be abandoned, only an exploratory procedure having been made. Such explorations were always a disappointment to the surgical team and to the patient; much work, anxiety, and expense accomplished nothing of value except establishment of the fact that the lesion was "inoperable." Fortunately, exploratory operations have now been reduced to a much lower figure; in our last 100 operations there have been but six (in two of these it was reasonably clear before operation that the condition was not amenable to surgical therapy). This reduction is largely due to the fact that grafts are now available for the treatment of certain situations which previously we would have called inoperable.

Age of Patients Operated Upon

The series of 270 operative cases includes children and adults; the distribution according to ages has been as follows:

0–10 yrs.	46 patients
11–20 yrs.	118 patients
21–30 yrs.	74 patients
31–40 yrs.	30 patients
41–50 yrs.	1 patient
Above 50 yrs.	1 patient

In adults, operations have generally been far more arduous than those in the childhood group. Fatality rates have been slightly lower in children than in adults, but the difference is not great.

Blood Pressure Changes

In evaluating postoperative states we are concerned most with objective evidence of what has been accomplished. Changes in blood pressure afford the best record of the readjustments which have been made in the circulatory system. The relief of hypertension is the main purpose of the surgical attack; observations indicate that it is possible to reach this goal in a high percentage of cases. Removal of an aortic block seldom gives a precipitous fall of the arm pressures. Though we have seen them return to normal within 24 hours, the more common reaction is to have a gradual distention of the vascular bed in the lower part of the body during the subsequent two to three weeks, and, concomitant with this, a progressive fall in the arm pressures. Generally,

the maximum benefit is manifested by the end of several weeks; if relief of hypertension has not been obtained in this period, it is usually wishful thinking to anticipate that it will occur in the more distant future.

Of our patients who have survived excision of a coarctation, follow-up studies have been made from two months to as long as seven years after operation. There has been no relief of hypertension in 2 per cent, a fairly satisfactory relief of hypertension in 10 per cent, and a complete cure of hypertension in 88 per cent (adults with arm pressures below 140, children with pressures lower than this, according to their age).

Postoperative Development of Aneurysm

Routine, long-term postoperative chest roentgenograms have not been obtained in all cases, but in those studies which we have made, no aneurysm has yet been found.

Postoperative Disruption

There has been only one death in patients after discharge from the hospital. This occurred in a 22 year old man who obtained a satisfactory relief of hypertension by removal of his coarctation. One year later there was sudden onset of chest pain and hemoptysis; the roentgenogram showed a fist-sized mass in the chest to the left of the spine which almost certainly represented a hematoma near the operative site. With bed rest, sedation, and transfusions the bleeding subsided, but a few weeks later there was a fatal hemorrhage. No autopsy examination was allowed. Whether the bleeding had come from a thin intercostal artery or from the aortic suture line is unknown.

Use of Aortic Grafts

We have employed aortic grafts in 37 patients. The age distribution of these subjects, and the percentage of cases in each age group requiring grafts were as follows:

1–10 yrs.	3 patients	6 per cent of cases
11–20 yrs.	11 patients	9 per cent of cases
21–30 yrs.	17 patients	23 per cent of cases
31–40 yrs.	6 patients	20 per cent of cases
Over 40 yrs.	0 patients	0 per cent of cases

The need for grafting in the child is uncommon; the call for it in adult patients is frequent. In the entire series of 270 patients treated for coarctation of the aorta, grafts were employed in 14 per cent. It is quite likely that the more liberal use of grafts would have improved the results in that group of patients who, because of a poor primary anastomosis and a lumen of suboptimal size at the junction, had only fair relief of hypertension.

Certain statements can be made regarding aortic grafting. There has been no sepsis in any case, a fact which we believe is due to meticulous care in collecting and handling the grafts. Three patients died while in the hospital, all from causes unrelated to the grafting. The survivors have been followed for periods of time varying from a few months to as long as five years. In no case has there been rupture of a graft; in no case has there been aneurysm formation. One subject shows roentgenographic evidence of calcification in the graft, but on clinical findings has an excellent aortic pathway. In no instance has there been any symptom or sign suggesting embolism from a graft site.

Viewed from the point of view of therapy for pre-existing hypertension, the over-all picture in the grafted cases has been very pleasing. The results can be classified as failure in one, good in two, fair in two, and excellent in 29. In the "excellent" group, the arm pressures have been restored to normal.

There can be no doubt that the ideal therapy for aortic coarctation is that in which the stricture is removed and a primary aortic anastomosis is made which establishes a lumen of completely normal size. However, sometimes it has been technically impossible to accomplish this; under such circumstances, the use of a graft has permitted treatment of a lesion which could not have been attacked by any other surgical means. Short-term observations of these human grafts up to five years have been extremely gratifying; no final conclusions should be made until the patients have been followed for several decades.

Finding of Aneurysm

In 21 patients an aneurysm was found either in the aorta just beyond the constriction, or

more commonly in the nearby portion of an intercostal artery just as it joined the aorta. These thin-walled lesions were considered to be a great hazard, because of the danger of rupture. It was therefore felt that they always demanded treatment. Because of the friability of the adjacent aortic wall, it was never possible to treat one of the intercostal aneurysms by removal of the mass and closure of the adjacent aortic wall. The aneurysms (intercostal or aortic) were managed by: (1) severing the intercostal artery proximal to the aneurysm and tucking in the aneurysmal sac with adventitial sutures, in seven cases; (2) excision of the aneurysmal segment of aorta and establishment of a primary aortic anastomosis, in three cases; (3) excision of the aneurysmal portion of the aorta and insertion of an aortic graft, in 11 cases.

Postoperative Paralysis

In two patients, aged 31 and 50 years, respectively, there developed during operation, spinal cord damage (probably from ischemia) which left these subjects with severe weakness and neurologic damage of both legs. This distressing complication places these two adults in a far worse condition after operation, (in spite of cure of hypertension) than they were in before. There was nothing at operation in the way of shock, obliteration of intercostal arteries, or other recognized factors that we could blame as specifically being the cause of these disasters. There may have been some abnormality in the anterior spinal artery or sclerosis of regional vessels which, when accompanied by the intrathoracic manipulations of operation accounted for temporary diminution in flow of blood to the spinal cord. These serious complications point out again the trials and tribulations of aortic surgery in adults in comparison with the more favorable results which are obtained in childhood and in the teen-ages.

Period of Recovery

Most patients have been discharged from the hospital 12 to 14 days after their surgery; occasionally they have had to remain as long as three weeks. They usually restrict their activity during convalescence for the subsequent two or three weeks. They have generally returned to full employment by six weeks after operation. Frequently patients have some pain, or discomfort, in the left shoulder or side of the chest which might require the use of codeine; such sequellae always disappear in a month or two. Limitation of motion in the left shoulder girdle clears up spontaneously in a few months.

General Observations

Following relief of an aortic obstruction there have been various findings in some—not all—patients which are worthy of note. When there had been headaches or epistaxes before operation, these have usually disappeared. When there had been cramps or weakness in the legs, these have vanished. Many patients have volunteered the information that their legs are warmer and now "beat" after operation, sensations which they had not previously experienced. Where there had been symptoms of cardiac embarrassment, these have been greatly improved by reducing the cardiac burden. Five of the adult females have subsequently passed through normal pregnancies and deliveries without any cardiac symptoms (one of them has gone through three pregnancies).

While surgical therapy for coarctation of the aorta has been available only since 1944, it is now quite evident that it rests on a sound basis and has a great deal to offer most persons who are afflicted with the abnormality. These operations are formidable undertakings which tax greatly the ingenuity and physical strength of the surgical team, but the efforts have been fully justified and rewarded by the results which have been obtained for the patients.

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SPECIAL ARTICLE

Report of Committee on Cardiac Catheterization and Angiocardiography of the American Heart Association

André Cournand, M.D., Chairman, Richard J. Bing, M.D., Lewis Dexter, M.D., Charles Dotter, M.D., Louis N. Katz, M.D., James V. Warren, M.D., and Earl Wood, M.D.

CARDIAC CATHETERIZATION and angiocardiography are two methods which are being widely used for the investigation of acquired and congenital heart disease. Since both of these procedures entail some risk to the patient, the Scientific Council of the American Heart Association deemed it advisable to establish a committee to evaluate this risk and to recommend methods to minimize it. The constituent members of the committee were chosen on the basis of their contributions to the evolution of these methods and experience in their application.

Method of Gathering Information for This Report

Two possible methods of gathering the necessary information were suggested: (1) To submit the experiences of the individual members of the committee for analysis; (2) to obtain information from all hospitals where the procedures were being used as to the qualifications of the principal and associate investigators, the adequacy of laboratory personnel and equipment, the number of patients studied, complications, fatalities, and other relevant facts. The first method was chosen because it was felt that evaluation of the experiences of a few laboratories, with a large number of patients, would more adequately reflect the possibilities and limitations of these methods than would a compilation of more data gathered from sources disparate in personnel, physical facilities and experience.

This report is based on the cumulative data of the members of this committee derived from approximately 5,700 right heart catheterizations in eight laboratories (table 1) and from angiocardiograms of 1,325 patients studied in two laboratories. It is divided into two parts: cardiac catheterization and angiocardiography.

Cardiac Catheterization

Catheters have been guided into the cardiac chambers via the venous and the arterial routes. The arterial route involves the introduction of the modified ureteral catheter against the current of flow, and includes potential injury to cardiac valves and heart, as well as injury to the vascular walls due to the force required to overcome local contraction of the arterial wall. The members of the committee are aware of individual instances of myocardial injury, torn aortic valves and introduction of the catheters into the coronary ostia resulting from this procedure. It is impossible at this time to make any specific recommendation except to urge extreme caution in the application of this experimental tool. These difficulties are much less likely to occur when the arterial catheter is not introduced into the left ventricle but is confined to the peripheral arterial system.

Subsequent remarks are confined to venous catheterization, which is established as a useful clinical tool.

Indications

The indications for venous catheterizations are difficult to establish since they will vary

with the interests of the investigator. In general, the method is currently used to complete the identification of specific congenital or acquired cardiac lesions, to establish their functional significance, to trace their physiologic course, and finally to evaluate the results of surgical procedures. The method has been extended to the investigation of the physiologic functioning of other organs in health and disease, such as kidney and liver.

TABLE 1.—*Survey of Right Heart Catheterizations and Fatalities in Eight Medical Research Units (Complete up to January 1952)*

Source of Information	Total No. of Catheri-zations	No. of deaths	Comments
University of Alabama & Johns Hopkins Hospital	1500	1	Autopsy revealed rhabdomyoma of heart.
Columbia University, Bellevue Hospital	900	1	Silicosis with tachycardia at rest; increased during severe exercise; cardiac asystole, autopsy negative.
Columbia University, Presbyterian Hospital	350	1	Mitral insufficiency; rigid catheter. Sudden pain in chest and death 2 hours after cathete ization while preparing to go home. Autopsy revealed subintimal hemorrhage in infundibulum, right ventricle.
Emory University	1550	0	
Mayo Clinic	312	0	1 Patient died during preparation for cardiac catheterization.
Michael Reese	287	1	Not definitely attributed to procedure
New York Hospital	192	0	
Peter Bent Brigham	600	0	

Contraindications

As with "indications," it is impossible categorically to define "contraindications." A contraindication in one laboratory may become the subject of study in another. There is no doubt that paroxysmal ventricular tachycardia constitutes an absolute contraindication to the introduction of a cardiac catheter. Similarly, the study of patients with recent myocardial infarction and subacute bacterial endocarditis will be associated with a considerable risk of accident and patient mortality due to the primary disease itself. Certain experiences of individual committee members are germane to this problem. Thus, manifestations of rheumatic activity clinically or by electrocardiogram constitute a contraindication for immediate study by catheterization in some laboratories. Recent pulmonary embolization is considered an absolute contraindication by others. All agree that investigation of a poorly cooperative or anxious patient usually results in a poor study with inconclusive results, particularly in procedures which require a steady state of circulation and respiration. Finally, a critically ill patient may be expected to tolerate poorly the preparations and manipulations incident to the procedure.

Complications: During Cardiac Catheterization

A. Arrhythmias: These constitute the most common complications. Premature ventricular contractions or short bursts of ventricular tachycardia are the most frequently encountered, and are most often observed when the tip of the catheter is passing through the tricuspid valve or is located in the right ventricular cavity. Consequently, exploration of the right ventricular cavity, using the catheter as a probe, should be restricted to a minimum; lodging of the catheter there should be avoided. Premature auricular beats, auricular flutter, auricular fibrillation, nodal rhythm, and other ventricular rhythms are seldom observed and are usually transient. Their incidence cannot always be related to any specific position of the catheter. Occasionally auricular arrhythmias have persisted for several hours after completion of the procedure, subsiding spontaneously or with the

aid of specific medication (digitalis or quinidine). All of these disturbances of rhythm are more apt to occur in the presence of congenital heart disease where considerable intracardiac manipulation may be necessary to localize the defect and factors such as anoxia may contribute to myocardial irritability.

B. Conduction Defects: The electrocardiographic pattern of right bundle branch system block is sometimes observed after the tip of the catheter has been advanced into the pulmonary artery. A shift in the position of the body of the catheter in the infundibular area may instantaneously arrest the apparent conduction disturbance. If the attack does not subside with change in the position of the catheter, the catheter should be removed.

It is important to recognize that disturbances in rhythm or conduction during cardiac catheterization may not be due to the venous catheter. Similar disturbances have been observed during introduction, and following placement of the arterial needle, with prompt subsidence following more adequate local infiltration with novocaine. Adequate anesthesia of the periarterial tissues will minimize the incidence of this complication.

C. Syncopal Syndrome: This syndrome is characterized by dilatation of the pupils, facial pallor, perspiration of the hands and upper lip, and yawning, associated with a bradycardia and hypotension. The investigator must always be on the alert to detect the appearance of these symptoms and either arrest the procedure or institute measures to obviate the symptoms. They may occur at any time during the procedure or shortly after its termination. Consequently, it is important to attend the patient even after the procedure is completed.

D. Venospasm: This complication is not unusual. It is manifested by pain above the operative site during manipulation of the catheter, and often subsides with cessation of manipulation. If it persists after infiltration of the site of insertion of the catheter with novocaine, the procedure should be terminated.

E. Loops and Angulations: These should not occur if the catheter is passed under continuous direct vision and if wide loops, especially in the auricle, are avoided. Advancement of the catheter should not be undertaken, even in the upper arm, without fluoroscopy, otherwise, knots may result which are resistant to attempts at uncoiling and may require surgical removal.

F. Trauma to Endocardium: Traumatic lesions of the endocardium have been noted as a frequent occurrence in animals but appear to be exceedingly rare in man. Postmortem examinations have been performed within hours, days and weeks of the procedure in patients who had died of their fundamental disease, or following surgery. In nearly all instances, no evidence of cardiac injury could be detected. However, in one instance of death following cardiac catheterization, an area of subendocardial injury was found in the infundibulum of the right ventricle. In this instance, the lesion could probably be related to the rigidity of the probing catheter.

It cannot be overemphasized that forcing the catheter forward against resistance in any area is to be avoided. The report of instances in which the catheter has been passed in the pericardial cavity, apparently by rupture through one of the cardiac veins, may be cited as emphasis on this particular point.

G. Pyrogenic Reactions: These complications were more frequent in the developmental days of cardiac catheterization. They may be completely avoided if proper care is exerted after catheterization to clean and rinse the catheter lumen, and if infusion sets are equipped with disposable plastic tubing rather than rubber tubing.

H. Air Emboli: These reactions too were more frequent during the earlier development of the method. Their consequences are more serious in the presence of congenital cardiac lesions with right to left shunt.

Complications: Miscellaneous

Specific complications may occur which are peculiar to the particular type of case under investigation. Thus, the cardiac catheter which causes no manifest obstruction or insufficiency of normal pulmonary valves, may in the presence of stenosis of the pulmonary valve precipitate acute anoxia due to impaired pulmonary blood flow.

A. Following Cardiac Catheterization: Local

irritation and thrombosis at the site of introduction of the venous catheter are probably related to the duration of the procedure and degree of manipulation, and are not rare. Fortunately these local thromboses have not been associated clinically with pulmonary infarction. However, pulmonary infarction has been frequently observed in the past in patients with mitral stenosis or pulmonary congestion following wedging of the catheter into a distal pulmonary artery branch for the recording of "pulmonary capillary" pressures. The complication of pulmonary infarction has been more of a problem in some laboratories than in others. The cause of this apparently true difference in the incidence of this complication is unsettled. In the chairman's laboratory this complication has been minimized by substituting autoclaving for chemical sterilization. Other investigators claim that prolonged occlusion of a terminal branch of the pulmonary artery in a congested lung bed may facilitate the occurrence of pulmonary infarction and that, therefore, wedging should be reduced to the practical minimum and probably should not exceed 10 minutes.

B. Fatalities: Four deaths have occurred incident to the 5,691 catheterizations. The members of the committee are aware that other deaths have occurred in laboratories not represented in this report, but for reasons indicated above, these deaths do not lend themselves to adequate analysis. Although no attempt has been made in this report to classify the patients according to the presence, absence and type of heart disease, it is apparent from the known interests of these laboratories that many of the patients had advanced heart disease and were particularly vulnerable to manipulative procedures of any type. This is emphasized by the death of one patient prior to introduction of the cardiac catheter while awaiting the start of the procedure. One of the three deaths that could be ascribed with certainity to the procedure revealed a rhabdomyoma of the heart at autopsy. A rigid catheter contributed to the death of another patient with subendocardial necrosis. Strenuous exercise in a patient with tachycardia at rest terminated in cardiac asystole in a third patient.

In summary, there was a mortality of less than 0.1 per cent in 5,691 cardiac catheterizations, and the possibility exists that, in the light of our present knowledge and experience, this mortality could have been further reduced.

C. Prevention of Serious Complications: Adequate sterilization and preparation of equipment and infusion prior to the procedure need no emphasis. During the procedure there is no better safeguard against serious complications than continuous clinical alertness and electrocardiographic observation. Any complaint of a queer or unusual feeling by the patient, a significant increase in heart rate, evidence of vagal stimulation, persistence of induced premature ventricular contractions or right bundle branch block, should lead, *without delay,* to termination of the procedure. Premedication with procaine amide or Nembutal are considered to be of no prophylactic value. It is further suggested that transit through the right ventricle should be minimized, and that pressure tracings from this chamber should be recorded only during withdrawal from the pulmonary artery. Mixed venous blood should be drawn from the pulmonary artery rather than right ventricle, except where the latter samples are essential to diagnosis. "Pulmonary capillary" pressures and samples should be obtained as rapidly as feasible.

The minor complications indicated above usually subside spontaneously following termination of the procedure. Arrhythmias which arise or persist following the termination of the procedure, should be managed as any similar spontaneous arrhythmia. The vasovagal reaction can usually be readily relieved by infiltration of the arterial site with more Novocaine, oxygen inhalation and the head-down position. In rare instances, it may become necessary to resort to the use of intravenous atropine for the treatment of this syndrome. Mechanical ventilators using oxygen, with facilities for delivering the gas under positive pressure, should be on hand for resuscitation. Procaine amide and quinidine are recommended for ventricular tachycardia. Digitalis glycosides, the specific ones varying with the individual preferences of the various laboratories, should be on hand for the arrest of paroxysms of auricular tachycardia or

fibrillation, especially when they are associated with heart failure. Morphine sulfate is advocated for the management of pyrogenic reactions.

However, the dreaded complications are cardiac arrest and ventricular fibrillation. The management of these complications has been of much concern, but the recommendations are fortunately largely theoretic, because of the rarity of these complicating catastrophes. For cardiac arrest there is no prophylaxis and poor prospect of treatment; surgical intervention and direct cardiac massage are advocated by some. The prophylaxis of ventricular fibrillation is the early elimination of the ventricular arrhythmias. When ventricular fibrillation occurs, various types of therapy are available. These include chemical defibrillation by means of drugs (procaine amide, procaine, quinidine) introduced via the catheter which should be removed into the superior vena cava, and various mechanical defibrillators. Once ventricular fibrillation has been established, the value of drug therapy alone is very doubtful. All methods of defibrillation are advocated with more optimism than experience.

Angiocardiography

The indications for this procedure and its limitations have been published elsewhere as isolated reports and included in a recent book. Although it is a potentially valuable diagnostic supplement in investigating anatomic alterations and defects in the heart and vascular tree, it is not an innocuous procedure and mere academic interest does not warrant its application. Diodrast is the most commonly used contrast substance, but the specific contrast medium has heretofore not influenced the frequency of undesirable reactions. At the New York Hospital, 1,256 patients were studied by means of 2,197 injections. This large number is the basis for our subsequent comments. The chief complication encountered was syncope, usually regarded as a manifestation of sensitivity. This sensitivity could not be predicted on the basis of skin or eye tests with the contrast substance. Syncope occurred most frequently in patients with congenital heart disease. Premedication did not seem to avert these attacks; drugs did not seem of help in relieving them. No need could be established for the electrocardiogram in this brief procedure. It is of considerable interest that in this large group of patients, there were no deaths, whereas in a group of 6,824 patients culled from 182 centers by correspondence, there were 26 deaths, predominantly in children with congenital cyanotic heart disease. Nearly all received epinephrine following the onset of the reaction but prior to death. The type of death was usually ascribed to respiratory arrest during, or immediately following, injection.

It seems reasonable to indicate that angiocardiography as a supplemental tool has considerable diagnostic potentiality, and should be used only in hospitals which can procure the elaborate equipment and trained personnel essential for the maximum yield of information. It is not an office procedure and at the present time, should be used to define lesions or disordered cardiovascular architecture about which information is necessary, but cannot be obtained by any simpler measures.

Summary and Conclusions

1. Cardiac catheterization and angiocardiography can supply, if properly applied, a considerable amount of diagnostic and physiologic information in human subjects, which is otherwise not available.

2. There is a definite risk of injury or death to the subject, which is influenced by the presence, type, and severity of heart disease. This risk can be minimized by adequate precautionary measures which can probably best be effected in large centers, utilizing specially trained medical and technical personnel.

3. It is worthy of emphasis that these methods can serve physicians best as a supplement to, rather than a substitute for, clinical and radiologic examination.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Ross, C. M., Wheeler, J. D., and Hagemann, P. O.: Escherichia coli Endocarditis. Arch. Int. Med. **90:** 258, (Aug.), 1952.

A patient is described who had *Escherichia coli* endocarditis superimposed on an old rheumatic valvulitis. This infection was uncontrolled during the initial weeks of intensive and combined antibiotic therapy. Oral therapy became impossible because of severe nausea and vomiting. Marked resistance on the part of the patient prevented use of a stomach tube, and thrombophlebitis and the threat of acute pulmonary edema seriously handicapped efforts at intravenous therapy. In spite of these handicaps, a "bacteriologic cure" was effected in this case.

Fatty metamorphosis of the liver, a lesion totally unrelated to the patient's heart disease, seemed to be the immediate cause of death. Presumably the hepatic insufficiency was the direct result of intensive Aureomycin therapy. While the outlook for patients with *Escherichia coli* endocarditis would appear to be improving with the advent of the newer chemotherapeutic agents, other factors limiting therapy may continue to keep recovery at a relatively low rate. In the present case, the endocarditis was apparently controlled by antibiotic therapy, the patient finally dying of hepatic insufficiency.

BERNSTEIN

BLOOD COAGULATION

Scholz, D. A., and Barker, N. W.: Preliminary Studies of a New Anticoagulant Drug. Proc. Staff Meet., Mayo Clin. **27:** 332 (Aug.), 1952.

Treburon is the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside and has a similar anticoagulant action to that of heparin. When administered intravenously or subcutaneously, Treburon prolongs the coagulation time of whole blood. Treburon has a potency about a fourth that of heparin, and the duration of action of the equiactive doses of Treburon and heparin are similar. Studies also demonstrated that the anticoagulant action of Treburon could be readily counteracted with protamine sulfate given intravenously. Treburon has only a slight effect on the prothrombin time and does not affect platelets, fibrinogen or sedimentation rates.

The coagulation time of the three patients who received Treburon sublingually did not seem to be affected. Serious toxic reactions were not observed during the course of the study.

SIMON

Volk, B. W., and Losner, S.: The Effect of Quantitative Variations of Anticoagulant Solutions upon Prothrombin Time. Am. J. M. Sc. **224:** 27 (July), 1952.

The authors have previously showed that the suspension of blood from dicoumarin-treated patients in anticoagulant solution (one part of 0.1 M sodium citrate or oxalate to nine parts blood) leads to a relative excess of the anticoagulant solution when compared with that found using normal blood. The present study was devised to test the sensitivity of the prothrombin measurement to changing concentrations of calcium in normal plasma by increasing the concentration of anticoagulant solution; and, to investigate the effect of reducing the concentration of anticoagulant solution in hypoprothrombinemic plasma. It was found that an increase in the concentration of anticoagulant added to normal blood produced a sensitivity to low concentrations of calcium chloride and increased the "optimum

prothrombin time." A decrease in anticoagulant solution added to hypoprothrombinemic blood decreased the sensitivity to low concentrations of calcium chloride and decreased the "optimum prothrombin time." Thus, erroneous estimations of the prothrombin level may result from inaccurate measurement of the quantity of anticoagulant solution.

SHUMAN

Russek, et al: Effect of Heparin in Cases of Coronary Insufficiency. J.A.M.A. 149: 1008 (July 12), 1952.

Reports of subjective improvement after administration of heparin in cases of angina pectoris suggested a study in which the effect of this drug on induced myocardial ischemia could be measured. Fourteen patients were selected who had varying degrees of coronary insufficiency and whose electrocardiographic response was constant during controlled periods with the Master two-step test. Intermittent administration of heparin in these subjects was without significant effect on the electrocardiographic response to standard exercise. The striking subjective improvement in anginal symptoms reported by others was not confirmed by the study.

KITCHELL

CONGENITAL ANOMALIES

Metianu, C., Durand, M., Guilemot, R., and Heim de Balsac, R.: Congenital Infundibular Aortic Stenosis. Presentation of Two Observations with Anatomic Verification. Cardiologia **21:** 106 (Fasc. 2), 1952.

The authors report two verified cases of congenital infundibular ("subaortic") stenosis found among a series of 1050 clinical observations and 90 autopsies of congenital malformation of the heart. The presented data pertain to the clinical picture, x-ray and angiocardiographic findings, the electrocardiogram and the anatomic features of this anomaly.

The anatomic findings were those described in the majority of previously reported cases; in one of the cases a patent ductus arteriosus was also present, in the other there was an abnormality of the aortic cusps. The most important radiologic sign was a pronounced enlargement of the left ventricle and to some degree also of the left atrium. The electrocardiograms in both cases presented distinct signs of left heart strain, termed by the authors "hypertrophy de type barrage" (resistance type).

The problems involved in a surgical approach and repair of the lesion are mentioned. In view of the hazards of such an operation, especially the danger of lacerating normal aortic valves, the authors feel that this type of anomaly should be attacked surgically only under direct visual control.

PICK

Bellet, S., and Gelfand, D.: Coarctation of the Aorta. Arch. Int. Med. **90:** 266 (August), 1952.

The occurrence of rupture of the aorta distal to the point of coarctation is a relatively uncommon complication of coarctation of the aorta. The pathogenesis of this lesion is believed to be the result of the continuous trauma of jets of blood ejected through the narrowed lumen of the coarctation with increased velocity. The "jet lesion" will not be produced if the narrowed orifice is directly parallel with the center of the aortic lumen. Unfortunately, as in this case, the narrow isthmus was situated at an angle with the longitudinal axis of the aorta, with the result that the increased velocity of the blood stream was continually directed in the form of a jet upon a small localized segment of the hypoplastic aortic wall situated 3 cm. below the constriction. It is not surprising, therefore, that a localized portion of the aortic wall subjected to the constant trauma of the jet of blood may be the initiating focal point for aneurysmal formation and/or rupture. The importance of recognizing such a lesion at operation is stressed because if incorporated in the suture line of the surgical anastomosis it would prevent adequate healing.

BERNSTEIN

Holling, H. E.: Compensatory Mechanisms for the Anoxia of Cyanotic Congenital Heart Disease. Clin. Sci. **11:** 283 (Aug.), 1952.

Compensatory mechanisms for the anoxia due to congenital cardiac malformations were investigated in 45 cases. The author shows that the ultimate cause of oxygen lack in cyanotic congenital heart disease is the fact that only a limited volume of mixed venous blood can be oxygenated in the lungs, and hence only a limited supply of oxygenated blood can be made available to the tissues. The oxygen supply to the tissues is determined not only by the arterial oxygen tension but also by the volume of blood reaching them. In severe pulmonic stenosis without septal defect, for example, the arterial oxygen tension is normal yet there is oxygen lack because the blood flow to the lungs is reduced as is the flow to the tissues. The effective pulmonary blood flow gives a useful measure of the degree of anoxia.

While there are several adaptations which may theoretically tend to compensate for anoxia, the author discusses evidence which favors three main mechanisms: (1) Increase in right ventricular pressure. As a result of increased cardiac work, more blood can be forced through a pulmonic obstruction and a normal cardiac output can be maintained despite the stenosis, or the effects of stenosis may be partially overcome. (2) Increase in oxygen utilization. The oxygen tension of the mixed venous blood of the author's group of patients was distinctly lower than in normal persons, with a mean of 30.1 mm. Hg compared with 40.5 mm. in normals. It is possible that increased utilization of oxygen in the

tissues may be brought about by the opening up of additional capillary vessels. The increase in oxygen utilization may even be great enough to compensate for a fall in the effective cardiac output from 3.2 to 2 L. per square meter per minute. (3) Increase in the oxygen capacity of the blood. This compensation has been noted only in those cases where the effective pulmonary blood flow is less than 2 L. per square meter per minute. Below this level the increase in hemoglobin concentration roughly parallels the decrease in pulmonary flow. This relationship is closer than that between the arterial oxygen saturation and hemoglobin concentration.

ENSELBERG

CONGESTIVE HEART FAILURE

Feltman, J. A., Newman, W., Schwartz, A., Stone, D. J., and Lovelock, F. J.: Cardiac Failure Secondary to Ineffective Bellows Action of the Chest Cage. J. Clin. Investigation **31:** 762 (Aug.), 1952.

Ventilatory studies were performed on two patients, one of whom had amyotrophic lateral sclerosis; the other had extensive calcific pleuritis of undetermined etiology. These patients both had defective bellows action of the chest wall. In both cases there resulted a reduction in vital capacity, maximum breathing capacity, and in effective alveolar ventilation manifested by high arterial carbon dioxide pressure and arterial oxygen unsaturation. Hypercapnia, anoxia, and polycythemia represented factors favoring medullary center damage. There was no evidence of significant intrinsic pulmonary disease. The authors discuss the possible sequence of events leading to cardiac failure in these patients. In the first patient, polycythemia may have led to hypoxemia. In the second, hypoxemia and secondary polycythemia resulted from the inefficient chest movement. Once polycythemia and hypoxemia have occurred, myocardial hypoxia and pulmonary hypertension lead to ventricular hypertrophy, dilatation, and failure.

WAIFE

Iseri, L. T., McCaughey, R. S., Alexander, L., Boyle, A. J., and Myers, G. B.: Plasma Sodium and Potassium Concentrations in Congestive Heart Failure. Relationship to Pathogenesis of Failure. Am. J. M. Sc. **224:** 135 (Aug.), 1952.

Many recent reports concerning plasma electrolyte levels in congestive failure have been regarded as inconclusive because of the prior use of mercurials in treatment of the patients. In the present study, plasma samples were obtained in 71 patients for electrolyte determination; of these, 56 had not received mercurials for two weeks prior to sampling. The remaining patients received mercurial injections during the preceding fortnight. All patients were free of renal disease, diarrhea or vomiting. The relationship of digitalis therapy to the results obtained is not discussed.

Increased plasma concentrations of sodium and potassium were found in the failure groups irrespective of whether left-sided or right-sided failure predominated. No correlation could be found between the blood urea nitrogen and the electrolyte levels. The sodium and potassium levels were somewhat higher in the more severe cases of failure. The effect of mercurial diuretics was to reduce the level of plasma sodium but not of potassium. Serial determinations during recompensation demonstrated a fall in plasma sodium whereas potassium levels declined only slightly. Refeeding of sodium led to increasing plasma sodium levels and slight to moderate gains in body weight which was increased by ambulation.

The findings are discussed in the light of osmotic interrelationships between cells and extracellular fluids. A rise in cellular osmolarity may be induced during failure leading to the transfer of sodium and potassium from the cell associated with cellular uptake of water. Circulatory, humoral, or intrinsic factors within the renal tubular cells cause retention of electrolytes and water. During partial recompensation or mercurial diuresis, cellular electrolytes are eliminated from the body without concomitant losses of cellular water thus reducing cellular osmolarity at the same time as hyponatremia develops.

SHUMAN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

De Stavola, W.: Fifteen Cases of Angina Pectoris Treated by Infiltration of the Preaortic Plexus (with Electrocardiographic Studies). Arch. mal. coeur **45:** 731 (Aug.), 1952.

The author used infiltration of the preaortic nervous plexus, a method first described by Arnulf, for the treatment of anginal pain in 15 patients. In seven of them pain had developed on an atherosclerotic basis, three cases had syphilitic heart disease, two had valvular heart disease, two had hyperthyroidism, and in one the cause of pain was not established. In the majority of cases pain disappeared, regardless of its etiology, and in eight cases electrocardiographic anomalies indicating coronary insufficiency were no longer found following treatment. The improved condition could be maintained by repeated infiltrations.

PICK

Nixon, R. K., Jr.: Association of Spontaneous Mediastinal Emphysema and Acute Myocardial Infarction. Report of Two Cases. New England J. Med. **247:** 310 (Aug. 28), 1952.

The cases of two men, aged 61 and 64 years, are described in detail. Spontaneous mediastinal emphysema was associated with an acute anterior myocardial infarction in one instance and an acute posterolateral infarct in the other. The experimental and clinical studies regarding the effects of spon-

taneous mediastinal emphysema upon the circulation are reviewed. It is suggested that the circulatory embarassment resulting from the extravascular compression of the systemic and pulmonary veins decreases cardiac output, results in pulmonary stasis and possible slowing of coronary blood flow. These effects may lead to myocardial ischemia and infarction, with or without coronary occlusion.

ROSENBAUM

HYPERTENSION

Leonard, J. C.: The Treatment of Hypertension: a Fifteen-year Follow-up. Yale J. Biol. & Med. **24:** 506 (June), 1952.

Fifty-two patients were followed for 5 to 15 years following operations for hypertension. Twelve had been subjected to subdiaphragmatic sympathectomy, and 40 had had lumbodorsal sympathectomy. There were only three survivors in the first group, and 16 in the second. In both groups, the blood pressure had returned to preoperative levels or higher within 6 to 24 months after operation, and there was little or no evidence of objective improvement. About half the patients were suffering from malignant hypertension.

The author suggests that in conducting a hypertensive survey, every effort be made to discover the existence of a curable cause for the hypertension, such as brain tumor, coarctation of the aorta, pheochromocytoma, adrenal cortical tumor and unilateral renal disorders. In reviewing the current therapeutic approaches to the problem, the author stresses the frequency with which almost any form of treatment, including placebos, results in temporary improvement. He suggests that following careful investigation of the patient, the order of treatment be directed along the following lines: psychotherapy, rest, sedation, weight reduction for the obese and low sodium diet for those with cardiac or renal involvement. Of less value are the veratrum alkaloids, methonium compounds and pyrogen therapy. Of least value are the surgical procedures of sympathectomy and adrenalectomy. The psychosomatic aspects of hypertension are particularly emphasized.

ENSELBERG

PATHOLOGIC PHYSIOLOGY

Welt, L. G.: Edema and Hyponatremia. Arch. Int. Med. **89:** 931 (June), 1952.

Each patient with edema and hyponatremia presents a particular problem that must be analyzed and evaluated in the light of the circumstances in which that patient may have acquired the hyponatremia. The most important data for this evaluation are derived from the history and clinical status of the patient. In particular, information should be sought concerning recent losses of fluid. Somnolence, clouding of consciousness, coma, falling blood pressure, and nitrogen retention all suggest an acute rather than a chronic dilution hyponatremia.

Once suspected, the diagnosis of hyponatremia can be established only by an analysis of the serum for the concentration of sodium. An estimate of the concentration of sodium from the concentration of chloride in the serum may be quite misleading. A decrease in the concentration of chloride in the serum may be a reflection of a respiratory acidosis or a metabolic alkalosis due to the loss of chloride in excess of sodium in response to a mercurial diuretic. In either instance the concentration of sodium in the serum may be quite normal. An estimate of the concentration of sodium from the sum of the concentrations of bicarbonate and chloride in the serum is less hazardous but may still be inaccurate. This is especially true when the nonprotein nitrogen of the blood is elevated and the concentration of undetermined fixed acids in the serum is increased.

If it is decided in any given instance to correct the hyponatremia in the patient with edema, this must be done with hypertonic saline solution. The concentration of sodium in the administered fluid must be greatly in excess of its concentration in the extracellular water, if the concentration of sodium in the latter is to be raised without producing a tremendous expansion of the extracellular compartment.

BERNSTEIN

Wetherbee, D. G., Brown, M. G., and Holzman, D.: Ventricular Rate Response Following Exercise during Auricular Fibrillation and after Conversion to Normal Sinus Rhythm. Am. J. M. Sc. **223:** 667 (June), 1952.

Older teaching, based on observations on resting patients, holds that auricular fibrillation is desirable in congestive failure because of the greater ease with which the effect of digitalis can be maintained and controlled. However, the studies described in this paper indicate that, following exercise, the peak ventricular rates in the fibrillating patients are high as compared with the rate after exercise in the same patient when normal sinus rhythm is restored. The resting pulse and post-exercise pulse was determined in 10 congestive failure patients who were experiencing auricular fibrillation, seven of these patients were receiving digitalis. The arrhythmia was stopped with quinidine in nine patients, and the other spontaneously reverted to normal sinus rhythm whereupon the observations were repeated. In every instance the peak ventricular response after exercise was greater during fibrillation than during normal sinus rhythm regardless of the presence or absence of digitalis. These findings suggest that auricular fibrillation impairs cardiac efficiency.

SHUMAN

Frieden, J., and Shaffer, A.: A Simple Method for Repeated Cardiac Output Determination in the

Unanesthetized Dog Using an Indwelling Cardiac Catheter. J. Lab. & Clin. Med. **39:** 968 (June), 1952.

A polyethylene tube or cardiac catheter is passed under fluoroscopic control through the external jugular vein into the main pulmonary artery. Polyethylene tubing has the advantage of a wide bore, but is more difficult to implant, being less flexible and not radiopaque. A metal plug at the tip with the hole in the tubing just proximal, permits visualization of its passage. When in place, the catheter is filled with heparin and closed at its proximal end with a metal plug, or is bent double over a short distance and tied. These were kept in situ and patent for periods up to four weeks, permitting daily withdrawal of mixed venous samples from the main pulmonary artery for determination of the cardiac output as often as one desires.

There was no evidence of ill health or infection among the animals used. There was no observed tendency for blood to diffuse from the pulmonary artery into the catheter between readings. If the catheter is flushed daily or every other day with saline and, when determinations are not taken, filled with heparin, it can be kept patent for two to four weeks or longer.

At postmortem examination, the sole lesions noted were occasional small mural thrombi in the right auricle. No valvular or pulmonary lesions were found.

MINTZ

Bessman, A. N., Alman, R. W., and Fazekas, J. F.: Effect of Acute Hypotension on Cerebral Hemodynamics and Metabolism of Elderly Patients. Arch. Int. Med. **89:** 893 (June), 1952.

Cerebral blood flow, cerebral metabolic rate, and cerebral vascular resistance were studied in 12 hypertensive patients over 50 years of age with evidence of cerebral arteriosclerosis before and after administration of tetraethylammonium chloride. Ten of the 12 patients experienced a fall in blood pressure of more than 30 mm. Hg. In these 10 patients, the cerebral vascular resistance decreased significantly, while the cerebral metabolic rate and cerebral blood flow remained statistically unchanged.

The data obtained suggests that most arteriosclerotic patients are able to compensate by vasodilatation for an abrupt hypotension of short duration, and thus maintain a stable total cerebral blood flow and cerebral metabolic rate. It is conceivable, however, that the compensatory mechanisms utilized would be inadequate in the face of more prolonged episodes of decreased blood pressure (for example, those occurring during sleep or induced by hypotensive agents), and studies are in progress to investigate this possibility.

BERNSTEIN

Rodbard, S., Katz, L. N., Reynolds, R. W., and Schack, J. A.: The Active Cardiovascular Dynamics of a Fistula Between the Pulmonary Artery and the Left Auricle. J. Lab. & Clin. Med. **40:** 136 (July), 1952.

The anastomosis of the pulmonary artery and left auricle produce acute cyanosis. No marked changes in the systemic arterial, pulmonary arterial and right and left auricular pressures occurred even with a pulmonary artery–left auricular shunt as great as 800 cc. per minute and lasting as long as seven minutes. These results are probably due in part to the fact that the resistance through the pulmonary circuit is normally so low that the provision of a shunt whereby pulmonary artery blood enters the auricle under a slightly higher pressure has no significant effect on the pulmonary artery pressure.

The absence of significant change occurred despite the decrease in arterial saturation to as low as 60 per cent. The reduction of oxygen saturation of the blood entering the coronary circuit gave no immediate evidence of significant deleterious effects on the heart itself. However, this effect may have contributed to the progressive development of the shock which was noted.

An increase in the intrapulmonary pressure produced by constriction of the air outlet by straining or coughing resulted in an immediate and marked increase in flow through the shunt. This suggests a mechanism for the syncope which is seen clinically in such cases. The increased flow of blood through the shunt caused a marked reduction in flow through the lungs, leading to hypoxemia and syncope.

There is no significant change in venous or arterial pressures in both the artificially produced pulmonary artery–left auricular shunt and the clinical condition of pulmonary arteriovenous fistula.

MINTZ

Guyton, A. C., Satterfield, J. H., and Harris, J. W.: Dynamics of Central Venous Resistance with Observation of Static Blood Pressure. Am. J. Physiol. **169:** 691 (June), 1952.

A special external venous circuit was used to study the effects of progressive resistance to return of blood to the heart. When the flow of blood was decreased toward zero it was demonstrated that arterial pressure fell slowly at first and then rapidly. Venous pressure increased slightly to approach arterial. "Static blood pressure" is the equilibrium pressure throughout the circulatory system when no blood is being pumped by the heart. This value is a limit which indicates the maximum effect of all circulatory pressures as heart action stops. The upper limit of static blood pressure as the result of impeded venous pressure alone is 6.0 mm. Hg with a heart totally stopped for a few seconds. When the point at which the vasomotor reflex has attained its maximum intensity is reached, the static blood pressure is 17.0 mm. Hg. Static blood pressures are increased by infusion previous to cardiac fibrillation. A 1 mm. Hg fall in right auricular pressure as a

result of progressive central venous resistance was accompanied by a 37 per cent decrease in cardiac output.

OPPENHEIMER

Prec, K. J., and Cassels, D. E.: Oximeter Studies in Newborn Infants During Crying. Pediatrics **9:** 756 (June), 1952.

The authors present a study of the influence of age on the change in oxygen saturation during crying in the newborn infant. The oxygen saturation of 135 normal full term infants ranging in age from one and a half hours to nine days was determined by the oximeter. Infants with delayed onset of respiration and those showing excessive amounts of mucus and amniotic fluid were excluded from the study. The subjects were divided into two groups; the first group included those up to 4 days of age and the second group, those 4 to 9 days of age. Group I showed a mean oxygen saturation during sleep of 94.94 per cent, and group II, 94.79 per cent. During crying the mean oxygen saturation was 93.2 per cent in group I, and 96.1 per cent in Group II. The mean changes from the sleeping level to crying level were small because both groups included increases and decreases. However, the changes were statistically significant. There was a tendency during the first three days of life for the arterial oxygen saturation to decrease during crying, while between the fourth and ninth day, the saturation tended to increase with crying.

Twenty-eight infants—15 in group I and 13 in group II—were studied while breathing oxygen in order to test the role of pulmonary function in the variations of oxygen saturation during crying. In oxygen the saturation during sleep increased from 98 to 104 per cent. The increases with crying were slight because of the high saturation. However, the decreases were similar in oxygen and in air.

It was concluded that the increase in oxygen saturation with crying which occurs most frequently in older infants is probably due to an increase in alveolar oxygen tension secondary to improved pulmonary ventilation during crying. The authors state that the paradoxic decrease in saturation during crying found in a large percentage of infants in the younger group is suggestive of the presence of a transitory V-A shunt. This shunt could either be through atelectatic areas of the lung or through the foramen ovale which is only functionally closed and can open whenever the pressure in the right auricle exceeds the left auricular pressure.

MARGOLIES

Bernstein, L. M., Foley, E. F., and Hoffman, W. S.: Renal Function during and after Diabetic Coma. J. Clin. Investigation **30:** 711 (July), 1952.

Renal hemodynamics was studied in six subjects during diabetic coma and at short intervals thereafter. Four of the subjects fell into a group with the same general pattern. During coma there was a reduction of all clearances. These were restored to normal or supernormal values a few days after correction of dehydration, acidosis and electrolyte deficits. These rapidly reversed alterations in function were believed to be caused by dehydration with its accompanying decrease in blood volume, cardiac output and renal blood flow.

In contrast, the other two subjects showed an azotemia which became more intense in spite of correction of the several deficits. There was a much slower return to normal values and renal function. In these subjects renal ischemia had apparently produced a reversible organic lesion similar to that found in "lower nephron nephrosis," except that it was milder and unaccompanied by initial oliguria.

WAIFE

Lukas, D. S., and Dotter, C. T.: Modifications of the Pulmonary Circulation in Mitral Stenosis. Am. J. Med. **12:** 639 (June), 1952.

Using the pulmonary "capillary" pressure as an approximation of the pressure in the left atrium and pulmonary veins, the authors present observations made before and after mitral commissurotomy in patients with mitral stenosis. As a result of the mechanical effect of the narrowed mitral orifice, circulation through the lungs is greatly modified in mitral stenosis. Hypertension in all segments of the pulmonary vascular bed develops as the consequence of the invariably present elevation of left atrial pressure. Cardiac output is reduced and relatively fixed. The flow resistance of the pulmonary arterioles is increased, causing an elevation of the pulmonary arterial pressure out of proportion to the pulmonary venous pressure and thereby accounting for a considerable portion of the increased pressure-work load of the right ventricle. The decrease in resistance after mitral commissurotomy suggests that physiologic, as well as previously described anatomic factors, are responsible for the arteriolar resistance. The hydrostatic pressure in the pulmonary capillaries is frequently equal to plasma colloid osmotic pressure and exceeds it during brief periods of exercise without development of frank pulmonary edema. This suggests that alterations in the alveolocapillary membrane tending to prevent formation of pulmonary edema are present in mitral stenosis. Tricuspid insufficiency without physiologic stenosis is found in approximately one-third of patients with mitral stenosis.

HARRIS

Folkow, B., and Gernandt, B. E.: An Electro-physiological Study of Sympathetic Vasodilator Fibers of the Limb. Am. J. Physiol. **169:** 622 (June), 1952.

Specific vasodilator fibers to muscular vessels of the hind limb have been conclusively demonstrated. These vasodilators are cholinergic. They are activated by electrical stimulation of a small area in

the supraoptic region. Stimulation of such an area increases venous outflow from the limb. At the same time there is increased electrical activity in the postganglionic nonmyelinated fibers to the limb. This activity consisted of slow potential waves in the peroneal nerve which appeared before blood flow increased and persisted throughout the time of excitation.

OPPENHEIMER

PATHOLOGY

Zucker, R., Leibowitz, S., Brody, H., and Sussman, R. M.: Perforation of the Interventricular Septum. Arch. Int. Med. **89:** 899 (June), 1952.

Reports on two patients with perforation of the interventricular septum in acute myocardial infarction, together with postmortem studies, are presented. The first patient died four and a half years after perforation had occurred, thus representing the second longest recorded survival. The observations on the first patient tend to confirm previous reports of the development of an apical diastolic murmur in the presence of a cardiac aneurysm.

In the second patient, the perforation was diagnosed during life and was secondary to infarction caused by atherosclerotic narrowing of an unusual septal branch of the left anterior descending artery. Seventy-seven cases of perforation of the infarcted interventricular septum have now been reported. In 29 the diagnosis was made in life. Diagnosis is based on the development of a systolic murmur and thrill, usually most intense in the third and fourth intercostal spaces to the left of the sternum, in a patient with acute myocardial infarction.

BERNSTEIN

Bothwell, T. H., van Lingen, T. Alper, and Du Preez, M. L.: The Cardiac Complications of Hemochromatosis. Am. Heart J. **43:** 333 (March), 1952.

The authors report a case of hemochromatosis in a young adult woman, the salient clinical findings being heart failure, premature beats, paroxysmal arrhythmia, skin pigmentation, amenorrhea and enlargement of the liver.

The cardiac symptoms were controlled with bed rest, digoxin, salt-free diet, mercurial diuretics and quinidine. Radioiron studies were performed and compared with an adult menopausal control subject with mild diabetes. Twenty-eight per cent was excreted in the feces during the first seven days after administration, in contrast with 74 per cent of the control. The level of radioiron in the blood reached a maximum of 3.5 per cent of the administered dose after a period of 30 days, as compared with 1.1 per cent in the control. In vivo counts showed a large deposition of radioiron in the liver and heart of the case reported, but none in the control.

In the present and previous studies, the authors have found that young subjects with hemochromatosis absorbed greater quantities of iron from the intestinal tract than do older subjects. The higher incidence of heart failure in the younger age group may indicate that the disease is present in a more acute form in which iron is being absorbed and deposited at a much accelerated rate. On this basis, the damage to the myocardium would not be related so much to the degree of iron deposition as to the rate. It would thus be possible to explain why patients with heavy iron deposition in the myocardium have shown no clinical signs of myocardial damage, while others with less iron deposition have had extreme and irreversible heart failure.

HELLERSTEIN

PHARMACOLOGY

Beck, I. T., and Boulding, J. E.: The Action of Angelica Lactones on the Toxicity of Digitoxin and on the Cardiac Irregularities Produced by Digitoxin and Barium. J. Pharmacol. & Exper. Therap. **105:** 203 (June), 1952.

The effects of α-β and β-γ unsaturated angelica lactones upon the cardiac actions of digitoxin was studied in cats. Simultaneous infusion of β-γ unsaturated angelica lactone with digitoxin did not alter the toxicity of the latter, but rapid injection of the lactone during digitoxin infusion induced premature ventricular fibrillation. Simultaneous infusion of α-β unsaturated angelica lactone with digitoxin also did not affect the lethal dose of the glycoside. Rapid intravenous injection of the lactone, however, did abolish the digitalis arrhythmias for a short period. This lactone also was capable of eliminating cardiac irregularities due to barium chloride infusion. The authors conclude that the regulating action of the lactone is not through simple chemical competition for the same receptors. α-β unsaturated angelica lactone should be included in the "cardiac depressant" group of agents.

SAGALL

Gold, H., Greiner, T., Mathes, S. B., Marsh, R. R., Warshaw, L. J., Modell, W., Kwit, N. T., Otto, H. L., Garb, S., Bakst, H., and Kramer, M. L.: Study of the Mercurial Diuretic, Thiomerin (Mercaptomerin) by Subcutaneous Injection in Patients with Congestive Failure with Special Reference to Local Reactions. Am. J. M. Sc. **223:** 618 (June), 1952.

The desirability of providing congestive failure patients with a suitable mercurial diuretic preparation which can be safely and repeatedly self-injected by the patient is stressed. Such a preparation exists in the form of mercaptomerin which was demonstrated by means of a diuretic bioassay method, developed by the authors, to be as effective in producing a diuresis following subcutaneous injection as the intramuscularly administered mercurials. Furthermore, the rapidity of onset of the diuresis was similar with both agents.

Observations were made on the incidence of systemic and local reactions after 676 injections of mercaptomerin in 209 patients with congestive failure. It was found that after several injections of this agent a significant number of patients manifested local reactions. In certain instances there was evidence of an acquired allergy to the drug. Single subcutaneous injections likewise produced local reactions. It was found that Mercuhydrin injected subcutaneously produced the same number of local reactions as mercaptomerin. It is possible that further changes in the latter preparation will reduce the incidence of local reactions and thus render it more satisfactory for subcutaneous self-injection.

SHUMAN

Penman, W. R.: The Use of a Cation Exchange Resin in the Management of the Fluid Retentions of Normal and Toxemic Pregnancies: Further Observations. Am. J. M. Sc. **223:** 657 (June), 1952.

Following the satisfactory use of cation exchange resin in the management of fluid retention in a group of hospitalized pregnant patients, the author applied the same therapeutic program in 26 edematous patients in the obstetric clinic. There were seven patients who were unable to take the resin because of nausea, vomiting or dislike of the drug. In nine of the patients, the program was only partially effective in reducing edema. In eight patients, there was complete loss of edema and a reduction of weight. One patient with severe rheumatic heart disease, who had become edematous, was satisfactorily treated with the resin and was maintained at "dry weight" throughout the remainder of the pregnancy. No clinical evidence of electrolyte disturbances or of acidosis developed in these patients. In one patient, resin therapy appeared to mobilize excessive amniotic fluid, but it failed to prevent the development of pre-eclampsia in two other patients.

SHUMAN

Baikie, A. G., and Smith, J. R.: A New Ganglion-blocking Agent: Trial of "Ciba 9295" in Man. Lancet **6719:** 1144 (June), 1952.

The authors gave this diquaternary ammonium dibromide intravenously to normal adult male volunteers, all of whom were patients awaiting operation in general surgical wards. They observed skin temperatures of great toes, thumbs and calves; oscillometric readings of one calf; pulse-rate and blood-pressure. The drug was given to 26 patients on 30 occasions, the dose being gradually increased from 0.3 mg. per kilogram body weight. No definite response was obtained with less than 1.0 mg. per kilogram; but with doses of 1 mg., 1.25 mg., and 1.5 mg. per kilogram a definite response was obtained on 18 of 22 occasions. Skin-temperature changes reached a maximum within twenty to sixty minutes of injection and were usually still above base-line values at the end of two hours.

Blood-pressures almost always fell on administration of the drug. The lowest readings were usually found within five minutes of injection and thereafter the blood-pressure returned slowly to base-line values. Oscillometric readings generally decreased slightly in amplitude. There was no clear correlation between blood-pressure and skin-temperature changes. Apart from transient increases at the time of injection no changes in pulse-rate were observed. Obvious sweating did not occur and in only a few cases was there slight flushing. The size of the pupils was unchanged and accommodation was never paralyzed. No postural hypotension was found at the end of the experiments.

BERNSTEIN

Blumberg, H., Schlesinger, A., and Gordon, S. M.: Toxicological Studies of a New Mercurial Diuretic: Mercumatilin (Cumertilin). J. Pharmcol. & Exper. Therap. **105:** 336 (July), 1952.

The acute toxicity of Cumertilin was determined intravenously in mice, rats and rabbits; intramuscularly in rats and rabbits; subcutaneously in mice; and orally in rats. The results indicated that the acute toxicity of this drug is about the same as that of the currently available mercurial diuretic compounds. Comparative tests for acute intramuscular toxicity in rats, acute subcutaneous toxicity in mice and chronic intramuscular toxicity in rabbits showed that Cumertilin was as toxic as meralluride and less toxic than mersalyl-theophylline. Local irritation produced by subcutaneous injection of Cumertilin in mice was the same as that from meralluride and mersalyl-theophylline, but less than that from mercurophylline.

SAGALL

Schallek, W.: Quinidine-like Activity of Thephorin. J. Pharmacol. & Exper. Therap. **103:** 291 (July), 1952.

A comparison of the effects of thephorin tartrate and quinidine sulfate were studied in a variety of experiments. Thephorin was found to be more active than quinidine in lengthening the refractory period of the isolated rabbit auricle, in raising the threshold for electrically-induced auricular fibrillation in cats, in reducing the duration of acetylcholine-induced auricular fibrillation in dogs, and in the protective action against epinephrine-induced ventricular premature contractions in dogs. Both drugs resulted in similar changes in the electrocardiograms of cats but Thephorin caused greater prolongation of the refractory period and less slowing of conduction than quinidine. Intravenous Thephorin caused a somewhat greater hypotension than quinidine in dogs. In mice, Thephorin is about twice as toxic as quinidine.

SAGALL

Cutts, F. B., and Rapoport, B.: The Routine Use of Quinidine in Acute Myocardial Infarction. New England J. Med. **247:** 81 (July 17), 1952.

The routine use of quinidine in acute myocardial infarction was evaluated by studying four groups of patients: (1) 55 patients who received no quinidine and served as a control, (2) 66 patients who were given 0.2 Gm. of quinidine sulfate four times daily from 8 a.m. to 8 p.m., (3) a group of 40 patients in which alternate subjects received 0.4 Gm. of quinidine every eight hours, and (4) a group of 50 patients in which alternate individuals received 0.6 Gm. of quinidine at the same eight-hour intervals.

Premature beats occurring more often than rarely were observed in one-quarter to one-third of the control and the treated patients on all dosage schedules. In those patients given quinidine the premature beats were abolished in one-quarter to one-half of the total so treated. Auricular fibrillation and flutter occurred in both treated and untreated patients. Quinidine seemed to have some regulating effect in those patients who developed auricular fibrillation or flutter, but the prophylactic value of the drug in regard to arrhythmias was felt to be difficult to prove and, at best, only moderate. There was no clear evidence that the routine use of quinidine altered the mortality rate appreciably in acute myocardial infarction, nor did it seem to reduce the incidence of sudden death. There was some evidence in this study suggesting that quinidine at the higher dosage levels increased the hazard of sudden death. Toxic effects from the drug were infrequent and mild, usually only slight diarrhea, nausea or vomiting.

ROSENBAUM

Frumin, M. J., Ngai, S. H., and Papper, E. M.: The Mechanism of Action of Desoxyephedrine on the Vascular Bed in the Limb of the Dog. J. Lab. & Clin. Med. **40:** 131 (July), 1952.

The effects of intra-arterial administration of desoxyephedrine (N-methyl-β-phenylisopropylamine) upon the rate of femoral arterial blood flow of dogs was observed and compared with those of epinephrine and norepinephrine under various conditions. An attempt was made to clarify the mechanism of the peripheral action of desoxyephedrine and to find an explanation for the phenomenon of tachyphylaxis and the reversal of the pressor action.

Desoxyephedrine caused a primary increase lasting about one minute, followed by a secondary decrease persisting five minutes in the femoral flow rate. Second doses given during the secondary decrease produced a greater increase followed by little if any decrease in flow rate. In the sympathectomized limb the initial dose of desoxyephedrine induced little if any increase but caused a profound and sustained secondary decrease in flow rate. Subsequent doses usually produced responses similar to those of the untreated resting limb. In the preparation treated with dihydroergotamine (D.H.E. 45), initial and subsequent doses of desoxyephedrine caused no significant change in flow rate.

Epinephrine and norepinephrine caused a marked decrease in flow rate which usually lasted one minute in both the untreated resting and the sympathectomized limbs. This type of response was unaltered when these amines were given during the phase of decreased flow rate following desoxyephedrine. The decreases in flow rate were greater with epinephrine or norepinephrine than when desoxyephedrine was used. In D.H.E. 45 treated preparations, epinephrine yielded a transient increase and nor-epinephrine elicited no response.

The mechanism of the vasoconstrictor action of desoxyephedrine could result from competition by this compound for the enzyme responsible for the destruction of the sympathetic mediator (possibly amine oxidase), thereby protecting the sympathetic mediator. Desoxyephedrine could cause vasodilatation by antagonizing the action of the mediator by "combining with the motor receptors and blocking them up." This latter combination does not activate the receptors.

MINTZ

Winder, C. V., and Thomas, R. W.: The Effect of Perfusion Pressure on Papaverine Vasodilatation in Rabbit Hearts. J. Pharmacol. & Exper. Therap. **105:** 282 (July), 1952.

The authors studied the coronary flow and ventricular contraction heights in saline-perfused rabbit hearts at various pressure perfusion pressures. Measurements were determined before and at the time of maximal coronary flow induced by administration of 1/200,000 papaverine HCl. Coronary flow without drug and contraction height with or without drug varied little with pressure changes. With papaverine the coronary flow increased strikingly with pressure increases with a decreased resistance to flow which indicated pressure-distention of small vessels and/or opening of additional ones. Statistical studies showed that the logarithm of the ratio of during-drug to predrug resistance is an efficient measure of vascular action at a given pressure.

SAGALL

PHYSICAL SIGNS

Dunlap, R. W., and Ivins, J. C.: Unusual Lesions of Sternum Associated with Shoulder Pain. J.A.M.A. **149:** 552 (June 7), 1952.

Abnormalities of the cervical part of the spinal column, lesions of the chest, coronary disease, diaphragmatic irritation, neurologic lesions and gallbladder disease are among the conditions commonly considered in the differential diagnosis of referred pain in the shoulder joint. The authors present three cases of disease of the sternum as a

cause of pain in the shoulder. The first case was that of a spontaneous fracture of the xiphoid process and the other two were degenerative lesions of the manubriosternal joint. All three patients were symptomatically relieved by surgical means. Each patient had a bizarre and complex set of symptoms and each patient reported subjective relief from surgical treatment of the sternal lesions.

KITCHELL

Gmachl, E.: The Problem of the Genesis of the First Heart Sound. Ztschr. Kreislaufforsch. **41:** 513 (July), 1952.

In order to clarify the mechanisms involved in the production of the first heart sound, the author compared data of the literature with the results of his own clinical, roentgenologic, electrokymographic and phonocardiographic investigations on the subject He arrived at the following conclusions.

The normal first heart sound is the result of vibrations which are set up by the sudden impact of the closed ventricular cavities upon its inert contents. Closure of the A-V valves occurs, under normal conditions, slowly and before the onset of ventricular contraction. Hence, this factor cannot be of importance in the production of the first sound; however, the closed A-V valves may participate in the above mentioned vibrations of the system of ventricular cavities. Auricular activity may give rise to vibrations of low frequency, outside the range of perceptibility by the human ear, and, therefore, cannot contribute to the acoustic phenomenon of the first heart sound. The same is true for vibrations of the large vessels which can be observed at the onset of ventricular ejection. Differences in the opinion of various authors are explained by the use of different systems of recording and disagreements in terminology.

PICK

PHYSIOLOGY

Welch, G. E., Bruce, R. A., Bridges, W. C., Johnson, A. D., Lehman, J. H., Nielsen, M., and Glenn, D.: Comparison of a New Step Test with a Treadmill Test for the Evaluation of Cardiorespiratory Working Capacity. Am. J. M. Sc. **223:** 607 (June), 1952.

This study represents a further effort to develop a simplified method for the measurement of the functional cardiorespiratory capacity in humans. A previously described technic involved the use of a treadmill and equipment not generally available to most physicians for the evaluation of physical fitness. The method described in this work involves having the patient step on and off a 9 inch step for 10 minutes or less at the rate of 20 steps per minute. Attached to the patient during the test are the electrodes of an electrocardiograph arranged in a designated fashion and a sphygmomanometer cuff. From the accumulated data collected before, during and after exercise, the physical fitness index is derived by use of a formula presented by the authors. The usefulness of these methods of evaluation of cardiorespiratory capacity are somewhat limited since it has been recognized that a normal person may have a low score if poorly motivated during the test, or a patient with an illness, if strongly motivated, may have a good score. It is apparent that the results obtained by such testing must be interpreted in the light of careful clinical study of the patient.

SHUMAN

Kester, N. C., Richardson, A. W., Green, H. D.: Effect of Controlled Hydrogen-Ion Concentration on Peripheral Vascular Tone and Blood Flow in Innervated Hind Leg of Dog. Am. J. Physiol. **169:** 678 (June), 1952.

The authors used intra-arterial injections of buffered solutions to vary the pH in either direction from 7.4. Rate of flow and lateral blood pressure was measured in the femoral artery. Nerve supply was intact. Alterations from 7.4 in either direction increased blood flow. Alkaline shifts had more effect than equivalent changes on the acid side. The opinion is expressed that other solutions with vasodilator properties may act by virtue of the changes in pH that they produce.

OPPENHEIMER

Girling, F., and Maheux, C.: Perpheral Circulation and Simulated Altitude. J. Aviation Med. **23:** 216 (June), 1952.

An initial series of experiments, using 12 rabbits, was carried out, in which the animals were taken to 30,000 feet or above without oxygen. The resistance to flow showed little or no change up to 20,000 feet, but there is an obviously significant increase in the resistance to flow from ground level to 30,000 feet, the increase being approximately 100 per cent of the ground level value. A second series of experiments was performed, in which the animals were taken to simulated altitudes but this time breathing 100 per cent oxygen. It was possible to take the animals up to 40,000 feet without signs of anoxia, but the limiting factor in this series was the abdominal distention which became apparent above 35,000 feet. As in the first series, the resistance to flow of blood showed some change up to 20,000 feet, but there is an appreciable increase in the resistance from ground level to 30,000 feet, once again about 100 per cent. A comparison of the values of resistance to flow at 30,000 feet with and without oxygen shows no significant difference, and this applies also to a comparison of the levels of the critical closing pressures at 30,000 feet with and without oxygen. These results indicate that there is an increased resistance to the flow of blood resulting from a reduction in the barometric pressure. That this is not due to anoxia is indicated by the

fact that this increased resistance is present whether or not the animal is breathing 100 per cent oxygen.

BERNSTEIN

RHEUMATIC FEVER

Winblad, S.: Studies on Agglutination of Sensitized Sheep Cells in Rheumatic Diseases. II. On the Nature of the Agglutinating Serum Factor, Acta med. scandinav. **142:** 458 (Fasc. 6), 1952.

This study is concerned with the "agglutination activating factor" present in the serum of patients with rheumatoid arthritis (RAS). Many properties of the RAS factor were studied. It was observed that the size of the sensitizing dose was of major importance in demonstrating the reaction. Since the sensitizing serum from rabbits immunized a long period for production of sensitizing serum gave higher agglutination than hemolysis titers, it was concluded that different antibodies are concerned in the two titers and that the agglutination factor is the one responsible for the RAS reaction. It was found that the reaction could be demonstrated with serum from immunized guinea pigs. The factor promotes agglutination in general, but it is not identical with antibody agglutination. Diluted rabbit serum inhibited the reaction in sheep cells not too strongly sensitized but guinea pig, horse and ox serum failed to exert this same inhibitory effect. From a serologic viewpoint, the RAS factor behaves, in certain respects, like Coomb's serum.

ROSENBAUM

Winblad, S.: Studies on Agglutination of Sensitized Sheep Cells in Rheumatic Diseases. I. Agglutination Titer after Primary Absorption of Serum by Sheep Cells. Acta med. scandinav. **142:** 450 (Fasc. VI), 1952.

The agglutinating power for sensitized sheep cells of the sera of 1,346 patients with various internal disorders was observed. The reaction was positive in 48 per cent of 314 patients with rheumatoid arthritis. It was positive in only 4 per cent of 276 patients with rheumatic fever. Positive reactions were also recorded in isolated instances of nephritis, periarteritis nodosa, bacterial endocarditis and ulcerative colitis. There was a rough correlation between the agglutination titer and the erythrocyte sedimentation rate. Somewhat higher titers were recorded in patients with long standing arthritis. A relative but not absolute agreement was found between the agglutination titer for sheep cells and the streptococcal agglutination titer.

ROSENBAUM

Logue, R. B., and Hurst, J. W.: Rheumatic Fever during the First Few Years of Life and Its Differentiation from Endocardial Fibrosis. Am. J. M. Sc. **223:** 648 (June), 1952.

Rheumatic fever occurring in 26 children at the age of 5 years or earlier was diagnosed by the characteristic findings of rheumatic infection or by the development of rheumatic heart disease after a long term follow-up. Autopsies obtained in four of the patients demonstrated rheumatic cardiac involvement. The predominant findings were those of valvular lesions or myocarditis as well as arthritic symptoms which occurred in 19 patients. In addition one case of endocardial fibrosis is presented with autopsy findings, and the important features differentiating this disorder from rheumatic myocarditis are enumerated. The absence of murmurs in the presence of congestive failure or evidence of cardiac dilatation and failure during the first six months suggests endocardial fibrosis, if congenital defects are absent. The presence of pericarditis, a rapid sedimentation rate, long-term survival, the development of aortic insufficiency, objective evidence of polyarthritis, chorea, or subcutaneous nodules favor the diagnosis of rheumatic fever. The presence of coarctation with large heart and congestive failure in the young age group suggests endocardial fibrosis.

SHUMAN

Bailey, C. P., Olson, A. K., Keown, K. K., Nichols, H. T., and Jamison, W. L.: Commissurotomy for Mitral Stenosis. J.A.M.A. **149:** 1085 (July 19), 1952.

Cerebral embolization as a result of the manipulations incident to mitral commissurotomy occurred in 5.1 per cent of 235 cases in which methods other than carotid obstruction were employed to protect the brain. Stellate ganglion block in addition to other medical measures was found to be of relatively small benefit in the treatment of 12 patients. Prevention of embolization of thrombotic origin is theoretically possible by utilization of the left superior pulmonary vein as a site of entrance into the left auricle. However, in 21 cases with obvious thrombosis of the appendage in which the technic was employed, there were two deaths directly related to the vein approach. Prevention of complications by occlusion of the innominate and left common carotid arteries is described and was used in 80 cases with no evidence of cerebral or peripheral emboli and no evident untoward by-effects. Although the series is small, the results suggest this technic may afford a reasonably safe and effective method for the prevention of cerebral embolization during operations performed within the chambers of the left heart. Results suggest that there may be effective available collateral arterial supplies to the brain, which will support its life for periods somewhat longer than required by this technic.

KITCHELL

Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long W. K., Mebane, J. G., and Ellis, L. B.: Studies in Mitral Stenosis. Arch. Int. Med. **89:** 970 (June), 1952.

A study is reported of the hemodynamic effects in the administration of ouabain intravenously to five patients with mitral stenosis. None of these patients had clinical right-sided heart failure or had had a history of congestive failure. They suffered from varying degrees of chronic dyspnea, and three of them were virtually incapacitated. The response to ouabain was variable and unpredictable, but all patients lacked the ability to increase their cardiac output primarily by a significant increase in individual stroke output for a given diastolic filling time.

This study shows the inadvisability of including patients with mitral stenosis in any general group with heart disease when considering the hemodynamic effects of therapeutic agents or other measures on the circulation, since mitral stenosis is unique in that it presents a mechanical barrier to the circulation which certainly modifies the results.

BERNSTEIN

Ravin, A., Slonim, N. B., Balchum, O. J., Dressler, S. H., and Grow, J. B.: Diagnosis of Tight Mitral Stenosis. J.A.M.A. **149:** 1079 (July 19), 1952.

Recent advances in surgical treatment have made the diagnosis of tight mitral stenosis important. Evidence is accumulating that mitral commissurotomy is of benefit and can be performed with comparatively low mortality in selected cases with tight mitral stenosis. Diagnosis can be made clinically on the basis of: (1) the presence of the typical diastolic murmur of mitral stenosis; (2) the absence of a loud apical systolic murmur indicative of mitral insufficiency; (3) the presence of an enlarged left auricle; (4) the absence of left ventricular enlargement. In the presence of the above findings corroborative features are a functional status of class 3 or 4, evidence of right ventricular hypertrophy, episodes of pulmonary edema, congestive failure or hemoptysis in the presence of a heart of only moderately increased size. Cardiac catheterization is of little value in the diagnosis.

KITCHELL

ROENTGENOLOGY

Martin, J. F., and Friedell, H. L.: The Roentgen Findings in Atelectasis of the Newborn, with Special Reference to Changes in the Cardiac Silhouette. Am. J. Roentgenol. **67:** 905 (June), 1952.

Inadequate initial expansion of the alveoli or a delay in this process in the newborn infant results in atelectasis, manifested by respiratory distress, cyanosis, tachycardia and collapse. The roentgenographic examination of the chest usually discloses: (1) abnormal lung densities, homogeneous or disseminated, often obscuring the sharp cardiac margins; (2) elevation of the diaphragm except when it may be depressed by emphysema or obscured by lung densities; (3) shifting of the mediastinum when there is preponderance of pulmonary involvement in one lung, widening of the mediastinum when there are diffuse or disseminated lesions present; (4) narrowing of the intercostal spaces with unilateral atelectasis, and asymmetric intercostal widening or narrowing with diffuse or disseminated lesions, and (5) enlargement of the cardiac silhouette.

Enlargement of the cardiac silhouette was at first attributed to the decreased height of the thorax associated with the pulmonary lesions, but a comparison of such measurements in atelectatic and normal infants revealed no significant differences in the length of the thorax. The authors, therefore, assumed that cardiac enlargement was genuine, and discussed possibilities which would account for cardiac enlargement such as anoxia, tachycardia and altered thoracic volume displacing blood from the lungs into the heart chambers.

SCHWEDEL

Ravin, A., and Nice, C. M.: The Angle of Clearance of the Left Ventricle. Ann. Int. Med. **36:** 1413 (June), 1952.

Based upon a method involving the use of orthodiascopy and the measurement of an apparent change in size of a small metal bar placed on the chest as the patient is rotated through the left anterior oblique position to a degree which will just permit the shadow of the left ventricle to clear the spine, the angle of clearance of this chamber was established. In 200 normal men, it was found to vary from 38 to 86, the average mean and mode was 63. The wide scatter obtained made it quite evident that there was no "normal angle" above which one might consider the angle abnormal. The correlation between the angle of clearance and the other data which had been collected was in the main disappointing, There was, as might be expected, some correlation between the transverse diameter of the heart and the angle of clearance. However, there were many instances of rather marked lack of correlation. This lack of correlation was most evident with anterior-posterior chest diameters at both extremes. With thin chests, the angle was higher than expected, and with deep chests it was lower. Because of the variations normally found, the angle of clearance at the present time can only be of value in following the changes which might occur in the same patient, and can not be used to diagnose the presence of left ventricular hypertrophy.

WENDKOS

Ash, R.: Position of Aortic Arch and Descending Aorta. Roentgenologic Signs in Childhood. Am. J. Roentgenol. **67:** 924 (June), 1952.

The author differentiates right aortic arch with descent on the right from the right aortic arch with a high crossing to the left, in the postero-anterior and right anterior oblique positions. In both situa-

tions the lower trachea and the barium filled esophagus are displaced to the left in the postero-anterior position. The descending aorta passing down on the left side can usually be identified within the cardiac silhouette as a shadow to the left of the vertebral column. In the right anterior oblique position the esophagus is displaced anteriorly by the right aortic arch with a high crossing to the left, while in the type with a right descending aorta there is no deviation of the esophagus either anteriorly or posteriorly.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Logan, A. L., and Turner, R.: Mitral Valvulotomy in Pregnancy. Lancet **1:** 1286 (June), 1952.

Two pregnant women with mitral stenosis, complicated by attacks of acute pulmonary edema, were subjected to mitral valvulotomy in the 4th month. In each case pregnancy continued uneventfully to a normal delivery.

BERNSTEIN

Munnell, E. R.: Six-fingered Glove for Mitral Commissurotomy. J. Thoracic Surg. **23:** 628 (June), 1952.

The author describes a six-fingered glove which is designed to obviate hemorrhage in the course of performing a commissurotomy. The third finger of a surgical glove is removed at its base, and it is then placed snugly over a test tube. A star is cut on the palmar surface of the recipient glove, approximately half-way between the thenar eminence and the index finger. The finger to be added and test tube are inserted through the incision to the desired position, and the base of the finger is cemented to the glove, using rubber cement. Then the tip of the added finger and the index finger are cut off, and small cuffs are turned and cemented.

The six-fingered glove is used in commissurotomy after the purse-string sutures are placed in the base of the auricular appendage and the tip of the appendage is amputated distal to a noncrushing clamp. The glove is put on over the standard operating glove, and then the guillotine knife is slipped through the added sixth finger and out the index finger. The end of the sixth finger is then closed tightly with two turns of a heavy silk ligature.

ABRAMSON

Saunders, J. W.: Controlled Hypotension during Surgical Operations. Lancet **1:** 1286 (June), 1952.

To obtain a dry operating-field in surgical operations the fall of blood-pressure produced with hexamethonium can be increased by applying a negative pressure to the legs. The anesthetist has better control over the blood-pressure, which can be promptly raised or lowered by decreasing or increasing the negative pressure on the legs.

BERNSTEIN

Kinmonth, J. B., and Hadfield, G. J.: Sympathectomy for Raynaud's Disease. Brit. M. J. **4773:** 1377 (June), 1952.

The clinical results of ganglionectomy and of preganglionic sympathetic section for Raynaud's disease are the same in the authors' series. The absence of unpleasant side-effects from preganglionic section makes it preferable to ganglionectomy. The similarity in results of the two operations suggests that nerve regeneration is not the chief cause of relapse after sympathectomy.

BERNSTEIN

Bailey, C. P., Glover, R. P., and O'Neill, T. J. E.: Transmyocardial Palpatory Surgery of the Heart. Canad. M. A. J. **66:** 529 (June), 1952.

Transmyocardial palpatory surgery of the heart may be defined as surgery within the beating, fully functioning heart either by the maneuvers of a finger inserted into a cardiac chamber, or by an instrument within the chamber guided by the intracardiac finger, or guided by a finger palpating the surface of the heart or an adjacent great blood vessel.

The field of transmyocardial palpatory surgery has grown so that it now embraces at least the following procedures: (a) digital dilation or incisional enlargement of the stenotic tricuspid valve; (b) localization and anatomic appraisal of infundibular stenosis within the right ventricle in cases of tetralogy of Fallot; (c) performance of commissurotomy of the stenotic mitral valve either by the incisional or the finger pressure technic; (d) correction of mitral regurgitation by the transventricular application of a pedicled pericardial graft; (e) application of a similar graft through the root of the aorta to control aortic regurgitation may be performed blindly (by simply passing it through the aortic wall). However, proper control of the graft would require that the left index finger be inserted into the left ventricle through an incision in the anterior wall over the outflow tract; (f) digital dilation of the stenotic aortic valve is usually not possible because of the extremely hard fibrosis and calcification which is usual. The high intraventricular pressure makes hemostasis difficult. However, it is occasionally possible to insert a flat knife or guillotine along the index finger to further exaggerate the tendency to bicuspid transformation of the aortic valve so often seen by cutting along the remaining two postero-lateral commissures. In addition to the correction of valvular deformities by "finger surgery," the correction of cardiac septal defects lends itself admirably to this technic; (g) the removal of intracardiac tumors of a benign type, particularly the so-called "myxoma" which arise from the auricular septum also

may fall into the classification of transmyocardial palpatory surgery.

BERNSTEIN

Janton, O. H., Glover, R. P., and O'Neill, T. J. E.: Indications for Commissurotomy in Mitral Stenosis. Am. J. Med. **12:** 621 (June), 1952.

A five stage functional and therapeutic classification provides a convenient yardstick for evaluation of the patient with mitral stenosis for surgery. Stage 1 includes those with auscultatory evidence of mitral stenosis but no symptoms. Stage 2 includes patients with dyspnea and fatigue under physical stress. Stage 3 includes individuals who, despite the best medical therapy, are constantly becoming worse. Stage 4 includes patients with constant congestive failure even with reasonably limited physical activity. Stage 5 includes patients with irreversible cardiopulmonary pathologic changes. Surgery is recommended for patients belonging to stages 2 to 4.

Over-all mortality in over 400 cases has been about 10 per cent. In cases treated at a reasonably early or moderately advanced stage of their disease, a mortality rate under 5 per cent has been maintained. Seventy-eight per cent of patients undergoing mitral commissurotomy have improved.

The authors discuss the selection of patients for operation under seven major categories. The typical history is one of progressive functional incapacity and repeated episodes of cardiopulmonary embarassment. Ease of fatigability is a frequent prodromal sign. The patient should be evaluated early for surgical intervention at the onset of fatigue and exertional dyspnea. The natural history of a disease as progressively malignant as mitral stenosis will usually preclude consideration of many patients over 50. The older the patient, the more rigid should be the criteria for selection of the patient.

The valvular lesion ideally should be "pure" mitral stenosis. An associated valvular lesion, such as mitral insufficiency, aortic stenosis or insufficiency, constitutes an absolute contraindication, especially if it expresses itself by an appreciable left ventricular enlargement or a wide pulse pressure. The predominance of mitral stenosis is assured by the historical pattern of progressive cardiopulmonary impairment, a normal sized left ventricle, left auricular and right ventricular enlargement, electrocardiographic evidence of right ventricular preponderance or no axis shift (never left ventricular preponderance), and evidence of increased pulmonary vascular hypertension. Roentgenologically the least amount of left auricular and right ventricular enlargement is desirable. Left ventricular enlargement should be absent or minimal.

The better the functional capacity of the patient, the more ideal is the candidate for surgery. Individuals with greatly hypertrophied and dilated hearts may be acceptable for surgery if these patients respond to medical therapy and their congestive failure can be controlled. Complications accompanying mitral stenosis require evaluation. Auricular fibrillation does not prognosticate a poor result. Embolic phenomena may be helped by commissurotomy and subsequent amputation of the left auricular appendage. Hemoptysis, an indication of pulmonary hypertension, may be helped. Active rheumatic fever or subacute bacterial endocarditis constitute absolute contraindications for cardiac surgery.

HARRIS

Miller, R. L., and Falor, W. H.: Surgical Approach to Coarctation of the Aorta Complicating Pregnancy. J. A. M. A. **149:** 740 (June 21), 1952.

From the point of view of the obstetrician, the authors found less than 50 reported cases of coarctation of the aorta, associated with pregnancy, and all articles written from this standpoint represent conservative pessimism. Therapeutic abortion with sterilization and cesarean section with tubal ligation are the two components of good treatment most often recommended.

The authors report a case of a 22 year old white primigravida whose coarctation was discovered late in her pregnancy. Delivery was made by means of laparotrachelotomy. Approximately 11 weeks after this procedure a transthoracic aortectomy with primary end-to-end anastomosis was performed. One year later the patient was delivered of twin fetuses by a second laparotrachelotomy. The authors feel that pregnancy complicated by coarctation of the aorta does not necessitate therapeutic abortion nor routine sterilization. Aortic surgery should be done if the diagnosis is made early in the pregnancy and no complications exist. If the diagnosis is made at term the patient should be delivered by cesarean section and aortic surgery should be done sometime after the sixth postpartum week. If the postoperative result is satisfactory, future pregnancies should be handled as though the patient had no cardiovascular defect.

KITCHELL

Pender, J. W.: Care of the Patient during Operation on the Mitral Valve for Stenosis. Proc. Staff Meet., Mayo Clin. **27:** 310, (July), 1952.

The selection of anesthetic agent is probably not as important as the depth of the anesthesia produced. Most anesthetic agents produce vasodilation in proportion to the level of narcosis, and, in patients with mitral stenosis who have a fixed cardiac output, vasodilatation results in a fall in blood pressure. Fortunately these poor-risk patients require only very small concentrations of ether to maintain the light stage of general anesthesia necessary for satisfactory conduction of this operation. They require less than average anesthesia and, if given an average

amount of anesthesia, they frequently will not survive the operation. The efforts to prevent a decrease in cardiac efficiency during the operation fall into two categories: (a) prevention of hypoxia of the myocardium, and (b) prevention of adverse cardiac arrhythmias.

Stagnant hypoxia of the myocardium is an ever present danger. Coronary blood flow is primarily proportionate to the blood pressure in the proximal aorta. Thus deep anesthesia, which frequently causes a fall in blood pressure in these patients, may jeopardize the adequate flow of oxygenated blood to the myocardium. Therefore, the first line of defense against stagnant hypoxia of the myocardium is to perform the operation under the lightest possible stage of general anesthesia.

It has not been any more possible to prevent all cardiac arrhythmias during operation on the mitral valve than to prevent all decreases in blood pressure. On the other hand, what constitutes an "adverse" cardiac arrhythmia is an unsettled question, even among cardiologists. The reason for not administering procaine-like drugs routinely is that, in addition to, or by virtue of, their ability to inhibit some cardiac arrhythmias, these drugs inhibit the myocardium. As has been explained, many of the patients are just barely able to maintain a minimal blood pressure during the operation, and any additional myocardial inhibition, no matter how slight, might make the difference between life and death.

SIMON

Ansbro, F. P., Black, J. J., and Latteri, F. S.: Postoperative Treatment of Peripheral Vascular Injury by Employment of Continuous Spinal Anesthesia Prolonged for Eleven Days. Am. J. Surg. **84:** 3 (July), 1952.

After reviewing the present knowledge of the nervous and humoral control of the peripheral circulation, the authors presented a case of a patient with traumatic thrombosis of the popliteal artery treated with continous spinal anesthesia. The thrombus was first removed and closure of the artery was accomplished over a number 12 T-tube. Then spinal anesthesia was begun in order to inhibit vasospasm, and this was maintained over a period of 11 days. Seventy-two injections were given through a Tuohy catheter inserted into the subarachnoid space at the level of L2 and L3 and advanced 5 cm. No untoward effects were observed during and following the procedure. The temperature of the toes of the involved limb rose in the period of anesthesia and remained so afterward. No signs of neuritic involvement occurred.

ABRAMSON

Bellegie, N. J., Seldon, T. H., and Judd, E. S., Jr.: Cardiac Massage for Cardiac Arrest during Surgery. Proc. Staff Meet., Mayo Clin. **27:** 305, (July), 1952.

Cardiac arrest may occur as ventricular standstill or ventricular fibrillation. Either type results in an ineffective pumping of blood, and each type demands its own treatment. It has been shown that if efforts are to be made to re-establish the cardiac beat, the ultimate outcome depends to a large degree on the duration of the cardiac standstill. The interruption of flow of blood through the brain for more than three to four minutes is likely to produce irreparable damage to the brain that is incompatible with normal life.

Cardiac arrest is an emergency that demands immediate treatment. The decision to open the thorax or to incise the diaphragm in order to establish cardiac massage must be made quickly and carried out promptly. The chance of performing this procedure on someone who might have recovered without massage must be accepted. It usually is not difficult to differentiate ventricular fibrillation and ventricular standstill. In the treatment of ventricular standstill, it is important to massage the heart for one to two minutes before any cardiac stimulant is injected. Electric shock appears to be a practical and effective method for treating ventricular fibrillation. Cardiac massage also may be required.

Neither highly specialized training nor elaborate equipment is required for the maneuver just reviewed. If the general surgeon waits until a thoracic surgeon is summoned, he will not save any lives. The general surgeon should be acquainted with the possibility of cardiac arrest; he should know what to do when such an emergency arises, when to do it and how to do it properly.

SIMON

Mason, R. H., and Stein, I. F.: A Case of Cardiac Arrest during Surgery with Complete Recovery. Illinois M. J. **101:** 317 (June), 1952.

Sudden cardiac stoppage during surgery usually is due to either cardiac asystole or ventricular fibrillation. Cardiac asystole is the most common type. It may occur without underlying disease. Carbon dioxide retention may be an important etiologic factor. Other factors are unreplaced blood loss, increased vagal stimulation, hypoxia, cardiac trauma or compression by retractors. Hypopotassemia may be an important etiologic factor. Successful treatment of either type of cardiac stoppage depends upon immediate recognition and early institution of the proper therapy. This consists of three steps. The first is restoration of the circulation by cardiac massage. The second step is maintenance of adequate flow of oxygen into the lungs and the removal of carbon dioxide. The third step is the use of drugs.

BERNSTEIN

THROMBOEMBOLIC PHENOMENA

Flasher, J., and Stephenson, W.: Peripheral Embolic Arterial Occlusion. Angiology **3:** 249 (June), 1952.

The management of peripheral embolic arterial occlusion, based, in part, on 212 patients seen at the Los Angeles County Hospital between 1940 and 1949, is discussed. The mortality associated with embolism is approximately 50 per cent, while more than one-half of the embolic occlusions affecting the lower extremities result in loss of the limbs. The importance of early diagnosis and treatment is stressed. According to the authors, the role of embolectomy in the management of arterial embolism has not yet been clearly defined. Anticoagulants and vasodilating procedures are, however, recommended.

WESSLER

Shapiro, D.: The Leriche Syndrome (Thrombotic Obliteration of the Aortic Bifurcation). Am. J. Roentgenol. **67:** 891 (June), 1952.

Six cases of the Leriche syndrome with typical histories, clinical findings, operative reports and abdominal aortograms are presented. Three of the six had coronary artery disease; three had hypertension; all six were males. The chief symptoms include: pain, easy fatigability and sensation of coldness of the lower extremities; absence of peripheral pulsation below the umbilicus; systolic murmurs over the aortic bifurcation and the external iliac arteries, presumably due to segmental narrowing of the lumen; symmetric atrophy of the extremities (global atrophy); trophic changes of skin and toe nails; insidious onset and slowly developing course; gangrene, in the terminal stages of the disease. Inability to obtain or maintain an erection occurs in one third of cases.

The diagnosis is made clinically and verified by aortography. The latter procedure offers information as to the site of the lesion, its extent, and the state of collateral circulation present. Surgical excision of thrombotic areas is recommended, also splanchnicectomy.

SCHWEDEL

VASCULAR DISEASE

Reese, H. L., Cullen, M. L., and Beyer, F. D.: Local Shifting of Blood in the Lower Extremities. J. A. M. A. **149:** 821 (June 28), 1952.

Using Kety's method of measuring calf muscle circulation by the clearance of radioactive sodium, a study was made of the shifting of blood in the lower extremities produced by direct heat and by intravenously administered Priscoline. Conclusions were drawn that: (1) local shifting of blood occurs in the lower extremity between the skin and muscles and between muscle groups; (2) when cutaneous blood flow is increased by administration of direct heat and Priscoline, muscle circulation is reduced; (3) the use of Priscoline in patients with intermittent claudication and peripheral skeletal muscle disorders has no physiologic basis; (4) effective circulation is decreased in antagonistic muscles by exercise.

KITCHELL

Edwards, E. A., and Leeper, R. W.: Frostbite. J. A. M. A. **149:** 1199 (July 26), 1952.

Seventy-one cases of frostbite of the extremities are analyzed. These cases were all soldiers under adverse combat situations in Korea. Personal factors important in the causation of the freezing were chronic vasospasm or hyperhidrosis, previous cold injury, wounding and possibly tobacco smoking. Three stages of the disease are described: (1) the acute (characterized by the freezing, thawing, blistering, and early necrosis); (2) the subacute (where the necrosis is resolved and the vasospasm and acrosclerosis start); (3) the chronic (when the vasospasm and acrosclerosis continue and pain and recurrent ulceration may occur). The most important single factor in the extent of necrosis seemed to be the duration of freezing after the initial symptoms. The use of sympathicolytic drugs in the acute stage seemed to have no effect on the outcome. Anticoagulants, used in only two cases, should have a more thorough trial. Sympathectomy seemed to hasten healing and is indicated when severe vasospasm or other vascular disease has existed prior to the freezing or when the frostbite has caused loss of a peripheral pulse. One should wait no longer than two years for spontaneous disappearance of symptoms before performing sympathectomy. It was not possible in these cases to predict accurately which patients would show the long lasting chronic effects.

KITCHELL

Wagman, O. H.: Sudden Blindness Due to Intracranial Vascular Accident. Simultaneous Bilateral Homonymous Hemianopia (without Sparing the Macula) Following Infarction of the Visual Cortex. New England J. Med. **247:** 7 (July 3), 1952.

The case of a man aged 77 years, known to have hypertension for some time is presented. The development of sudden, total and permanent blindness due to bilateral infarction of the visual cortex is described. The occipital lobes were presumed to be the sole site of disease due to disease of the posterior cerebral arteries or the basilar artery. This is designated as an example of pure cortical blindness. The syndrome is unaccompanied by objective ocular or neurologic abnormalities. In this instance central vision was also lost, but in this rare disorder the macula is sometimes spared. The pupillary reflexes to light and convergence are spared since the lesion is above the primary visual centers. The patient died of a second cerebrovascular accident 20 months after the attack of blindness.

ROSENBAUM

Ballon, H. C.: Superior Vena Caval Obstruction. Ann. Surg. **136:** 39 (July), 1952.

The author presents the clinical story of a female patient manifesting signs and symptoms of obstruction of the superior vena cava. The etiologic factor was considered to be a partially calcified mediastinal mass located at the level of the right first and second

anterior ribs. Despite the use of several diagnostic procedures, the basis for the tumor could not be determined.

The symptoms consisted of a tightness in the neck, a choking sensation and swelling of the face. All complaints were exaggerated by such movements as those used in waxing the floor, bending over and cleaning the bath. Physical examination revealed marked distension of the neck veins in the recumbent position and elevated venous pressure in both arms. Intravenous injection of Diodrast showed complete obstruction of the superior vena cava at the level of the mediastinal mass.

ABRAMSON

Tocker, A. M., and Langston, H. T.: The Perivascular Space of the Pulmonary Vessels. J. Thoracic Surg. **23:** 539 (June), 1952.

The authors attempted to demonstrate the perivascular space around the pulmonary vessels of dogs, using gross, microscopic and roentgenographic methods. A small length of polyethylene tubing was introduced into the cleavage plane between the pulmonary vessel walls and the surrounding tissues at the hilum of the lung, and 10 to 20 per cent bismuth oxychloride solution was injected under moderate pressure.

The material was found to follow a readily identifiable perivascular space about the pulmonary vessels. It was believed that information regarding the nature and extent of the spaces was of great practical value in performing pulmonary resections in clinical cases, as well as in explaining pathologic processes in certain abnormalities of the lungs.

ABRAMSON

Cook, D. L., Ray, R., Davisson, E., Feldstein, L. M., Calvin, L. D., and Green, D. M.: The Effects of Cholesterol Dosage, Cortisone, and DCA on Total Serum Cholesterol, Lipoproteins, and Atherosclerosis in the Rabbit: J. Exper. Med. **96:** 27 (July), 1952.

The effects of cholesterol dosage, cortisone and desoxycorticosterone acetate on total serum cholesterol, lipoproteins, and atherosclerosis were studied over a period of 112 days in 32 rabbits. All three classes of lipoproteins increased with cholesterol feeding. Lipoprotein and total serum cholesterol concentrations were significantly and equally well correlated with the severity of atherosclerosis. Cortisone administration in the normal rabbit increased the concentrations of total cholesterol and of lipoprotein components of the S_f 10–15 and S_f 16–30 classes, but did not produce atherosclerosis. Cortisone treatment in cholesterol-fed rabbits did not produce atherosclerosis. Cortisone treatment in cholesterol-fed rabbits did not significantly affect the levels of serum lipoproteins, cholesterol concentration, or atherosclerosis produced by a 1.0 per cent cholesterol diet alone. Values for total cholesterol and S_f 5–9 class of lipoproteins in desoxycorticosterone acetate-treated animals were lower than those in controls but the degree of atherosclerosis was not significantly less.

BERNSTEIN

Kunkel, H. G., and Slater, R. J.: Lipoprotein Patterns of Serum Obtained by Zone Electrophoresis. J. Clin. Investigation. **31:** 677 (July), 1952.

The authors describe in detail their experiences with a method of zone electrophoresis applied to serum lipoproteins. This method has the advantage over other electrophoretic systems in that the components can be isolated directly so that lipid analyses can be carried out. Lipoprotein curves were obtained and the relative mobilities of α- and β-lipoproteins were correlated with the mobilities of the other serum proteins. The cholesterol-phospholipid ratio of the two major components were in agreement with the results obtained by chemical fractionation. Marked variations were found in pathologic sera with elevated lipid concentrations. These had, in general, a tendency to a diminution of α-lipoproteins and either an increase in the β-type or the appearance of a large component with an abnormal mobility.

WAIFE

Cazals, F., and Roy. A.: Communication between Aorta and Pulmonary Artery Consequent to Penetrating Trauma by a Sharp Weapon. Arch. mal. coeur **45:** 522 (June), 1952.

A 31 year old man suffered a stab wound of the left upper chest which was followed by the development of a hemothorax and rapid recovery. Two months later he developed dyspnea and congestive heart failure. Enlargement of the heart and a loud continuous systolic-diastolic murmur in the left subclavicular region suggested the presence of an arteriovenous shunt confirmed at cardiac catheterization, which also revealed a marked increase of pressure and oxygen saturation in the main pulmonary artery. The patient died from progressive heart failure one month later. Autopsy showed a traumatic communication between aorta and pulmonary artery, which resulted in enlargement of all four heart chambers. It is pointed out, that this rare clinical-anatomic observation may serve as example of the importance of hemodynamic factors in the pathogenesis of heart disease and of cardiac failure.

PICK

OTHER SUBJECTS

White, P. D.: Heart Disease Forty Years Ago and Now. J. A. M. A. **149:** 799 (June 28), 1952.

Dr. White feels that despite the disturbed state of the world at present and the increase in the

prevalence of heart disease, physicians and patients can look back over the last 40 years with much satisfaction, and forward to the next 40 years with hope and confidence.

He discusses the change in diagnosis, treatment and prognosis from 1911 to the present day. The establishment of cardiovascular diagnosis by etiology 30 years ago was extremely important. Patients with congenital heart disease considered hopeless in Dr. White's student days are not so regarded today. Probably 50 per cent of them can either be completely cured surgically or much benefited. Rheumatic heart disease is being controlled in such a manner that we may expect in another generation there will be little of it seen. The mortality from subacute bacterial endocarditis has been reduced from almost 100 per cent to about 20 per cent because of the use of penicillin, streptomycin and other antibiotics. Thyrotoxic heart disease is practically extinct, and syphilitic heart disease is disappearing. Hypertensive heart disease can be controlled in many cases by various measures, and it is now recognized that the patient with coronary heart disease may be in good health 10, 20, or more years after a serious myocardial infarction. Dr. White feels that research must be continued, not only basic research in the laboratory, but medical research in the clinic. The prevention of disease is of primary importance. The new research facilities in various universities are discussed, and stress is laid on the importance of fostering private enterprise and in coordinating all workers in the fields of both private and public health.

KITCHELL

Schwartz, B., and Berman, B.: Incidence of Heart Disease in Mass X-ray Surveys. J. A. M. A. **149:** 734 (June 21), 1952.

The authors examined chest x-rays of 10,549 persons made in the early part of 1949. Some abnormality of the cardiac silhouette was noted in 486 (4.5 per cent). From this group of 486 a total of 207 were selected at random and given complete physical examinations. Of this group 177 were found to have some form of cardiovascular disease. One hundred seventeen had hypertensive heart disease. Ten had hypertension alone, and 17 had rheumatic heart disease. Fifty-five had cardiac enlargement and six had aortic aneurysms. Sixty-two patients had well defined electrocardiographic abnormalities. Forty-eight per cent of the group did not have definite knowledge of heart involvement, and 52 per cent had previous knowledge of their heart condition. The pilot project consumed over 1000 hours of the collected efforts of the clinic staff for the 207 patients, an average of five hours being devoted to each patient. This type of service is expensive but the incidence of heart disease is so significant that some type of follow-up is imperative in mass x-ray surveys.

KITCHELL

Rich, C., Jr., and Webster, R.: The Natural History of Uncomplicated Syphilitic Aortitis. Am. Heart J. **43:** 321 (March), 1952.

The authors report a series of 141 patients in whom the clinical diagnosis of uncomplicated syphilitic aortitis was made. All patients with coronary ostial stenosis, aortic valvular insufficiency or saccular or fusiform aneurysm at the time of the original diagnosis were excluded. The diagnosis was accurate in 39 of 46 cases as demonstrated by autopsy findings, subsequent development of other evidences of cardiovascular syphilis or angiocardiograms. The average age at diagnosis was 51 years.

The signs most useful in making the diagnosis of aortitis were: (1) x-ray evidence of aortic dilatation in 122 patients; (2) accentuation of the aortic second sound in 68 patients; (3) submanubrial dullness in 52 patients; and (4) an aortic systolic murmur in 78 patients. Electrocardiograms, symptoms, pulse pressure changes and heart size were not useful in making the diagnosis. Angiocardiograms were positive in 20 and negative in five patients. One of the latter developed aortic insufficiency at a later date. The prognosis was not affected by the age of the patient at the time of the diagnosis of aortitis, or by the subsequent development of aortic insufficiency or aneurysm (15 per cent of the series).

The patients were followed for an average of 7.1 years, 62 per cent for more than five years, and 41 per cent for over 10 years. The death rate was no greater in the group followed 10 years and more (12 per cent) than for the other groups. There was a lower death rate in the adequately treated group.

The authors conclude that the diagnosis of uncomplicated syphilitic aortitis can be made clinically with reasonable accuracy and carries a favorable prognosis.

HELLERSTEIN

Samuelsson, S.: Cor Pulmonale Resulting from Deformities of the Chest. Acta med. scandinav. **142:** 399, 1952.

The author reports the study of 41 living patients and 62 deceased subjects who had severe spinal deformity causing distortion of the thorax. Of the living patients, one-half showed signs of cor pulmonale; the electrocardiograms in 37 per cent showed right cardiac strain, 19 per cent showed signs of left heart strain, and roentgen signs of right heart strain were observed in 27 per cent. Sixty-three per cent of the patients who were deceased had shown signs of cor pulmonale. Fifty-nine per cent of them died of heart failure, and pneumonia was the cause of death in 14 per cent. One patient died a few hours after administration of a local anesthetic, and a second patient died four hours after an injection of morphine given for cardiac failure. The author emphasizes that morphine is contraindicated in all cases of spinal deformities showing signs of cardiac or pulmonary failure.

ROSENBAUM

Platt, R.: Structural and Functional Adaptation in Renal Failure. Brit. Med. J. **4773:** 1372 (June), 1952.

The author has shown that most if not all the functional disturbances known to occur in human renal failure are precisely those which occur in animal experiment as a result of reduction in the amount of functioning renal substance—that is, loss of nephrons. The concept of renal failure should not be one of disordered function, but rather one of extremely efficient function by a renal remnant now too small for its task.

BERNSTEIN

Zeman, F. D., and Storch, S.: Syphilitic Heart Disease in the Aged. Ann. Int. Med. **36:** 1423 (June), 1952.

The present report is based on the findings in 36 cases of syphilitic heart disease, 60 years old and over. The diagnosis of cardiovascular syphilis was confirmed or established at autopsy in 14 cases, and was made on clinical grounds in 22 cases. Twenty-eight cases were encountered in the seventh decade and nine in the eighth. Positive serologic tests were obtained in eight of the 14 autopsied cases, and in 18 of the remainder. Acute heart failure either with or without chronic heart failure was present in 8 out of 14 autopsied cases and in 14 of the remainder. A good clinical response to therapy for failure was observed in many of the cases seen clinically. Some of the cases were associated with evidences of congenital, hypertensive, arteriosclerotic and rheumatic heart disease. Two cases of subacute bacterial endocarditis grafted upon syphilitic disease of the aortic valve are included in this series. In six cases, there were combined syphilitic and rheumatic lesions, and, of this group, two showed the association of syphilitic aortic insufficiency and aortic stenosis presumably rheumatic in origin. Arteriosclerotic aneurysms of the thoracic or abdominal aorta were encountered in conjunction with syphilitic heart disease. Auricular fibrillation, however rare among younger patients, was observed in 7 out of the 36 patients. The correct diagnosis of syphilitic heart disease would be arrived at more frequently in older individuals if the physician regularly considered syphilis as a diagnostic possibility in every case of heart disease and proceeded after a careful history and thorough examination to have the heart and aorta examined roentgenologically and the blood tested serologically.

WENDKOS

Samuelsson, S.: Chronic Cor Pulmonale in Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Pulmonary Emphysema, Acta med. scandinav. **143:** 15 (Fasc. I), 1952.

A series of 363 patients with bronchial asthma, chronic bronchitis and pulmonary emphysema were reviewed. Two hundred and eighteen of them were found to have electrocardiographic or roentgen evidence of cor pulmonale. The older patients were more apt to show definite abnormalities, but the duration of symptoms was the same for the groups of normal and abnormal patients. The major clinical findings were dyspnea, orthopnea, cyanosis and chronic disability. The author mentions the difficulty of early diagnosis of heart failure in these patients because of the confusion of pulmonary and cardiac factors, but it is emphasized that dyspnea at rest in a patient suffering from uncomplicated emphysema must be considered the first sign of decompensation.

Slightly less than one-half of the 218 cases showed some electrocardiographic abnormality. These changes included right axis deviation, increase in the size of P_2 and P_3, changes in T_2 and T_3, inversion of the T waves in the parasternal lead, R′ deflections in the parasternal lead, changes in the S-T segments in leads II and III, right bundle branch block, or low voltage in the standard leads. Roentgenographic abnormalities observed in one-third of the cases included prominence of the pulmonary arch, right cardiac enlargement, or increase in the width of the right or left pulmonary artery.

Twenty-three patients in addition to the larger series were known dead and 21 of them had been examined postmortem. Hypertrophy of the right ventricle was present in 71 per cent of this group. Electrocardiograms had been abnormal in 10 but normal in two who had cor pulmonale. Roentgen studies in eight who had postmortem evidence of cor pulmonale had been abnormal in five and normal in three. The hazard of morphine administration in cases of cor pulmonale is emphasized by the author.

ROSENBAUM

Chapman, J. S.: Pulmonary Infarction. Southern M. J. **45:** 597 (July), 1952.

The clinical features of pulmonary infarction are: (1) hemoptysis; (2) sudden chest pain, preceding a rise in temperature; (3) temperature, pulse and respiration in intermediate range; (4) temperature characteristically of five days' duration, or appearing in bouts of similar duration, unaffected by antibiotics; (5) usually moderate leukocytosis with moderate left shift; (6) sedimentation rate moderately elevated, with a rapid return to normal; (7) jaundice; (8) electrocardiographic signs; (9) leg signs, previous injury, previous thrombophlebitis, and so on; (10) sterile fluid with gross or microscopic red blood cells; and (11) freedom of sputum from pus or mucus.

Roentgenographic features of pulmonary infarction are: (1) peripheral location with convex or humped border toward the hilum; (2) long axis of infiltration parallel to longest axis of adjacent pleura; (3) aerated areas of tissue between adjacent areas of consolidation; (4) multiplicity of infiltrations; (5) appearance of thin, diagonally directed, intra-

pulmonary lines, usually within three or four days; (6) rapid variation of roentgenographic shadows, location, character, number; (7) early or immediate appearance of pleural fluid; and (8) rapid resorption of consolidation.

The diagnosis of pulmonary infarction may be attended with great difficulty, and no completely reliable feature or group of features will serve to make a positive diagnosis in every instance. In view of the dangers of the condition, if infarct cannot be excluded, the patient should be treated as though the diagnosis were established.

BERNSTEIN

Frankel, A. L., and Rothermich, N. O.: Clinical Experiences in Ballistocardiography. Ann. Int. Med. **36:** 1385 (June), 1952.

At the present time, it must be considered that the usefulness of the ballistocardiograph in routine medical practice is highly questionable. If such a procedure is useful, its range of usefulness must be very narrow indeed. There are characteristic abnormalities in the ballistocardiographic curve, which result from coarctation of the aorta, or aortic insufficiency, but these conditions can be diagnosed without the ballistocardiograph. Abnormalities in the ballistocardiographic pattern occur in patients with hypertension only when the hypertension is of such severity as to produce cardiac damage recognizable by other means. It is entirely possible that the ballistocardiograph may prove of extreme value in the diagnosis of otherwise occult coronary arteriosclerotic heart disease. In addition, this newer technic might be advocated as a method of observing the effectiveness of therapy in certain cardiovascular conditions and as a guide in the progressive ambulation of cardiac patients. In the final analysis, the real clinical usefulness of this instrument will be determined from its wider application in medical practice.

WENDKOS

Glomset, D. J., and Cross, K. R.: Morphologic Study of the Cardiac Conduction System. Arch. Int. Med. **89:** 923 (June), 1952.

Because of the abundance of nerve elements in all hearts examined, the authors decided to investigate the intrinsic nervous system of the heart to determine, if possible, its relation to impulse formation and conduction. This communication deals with the development of knowledge concerning cardiac conduction, the topography of the cardiac nerve elements, and the nerve endings on muscle cells.

The authors were especially interested in the plexuses within the myocardium. All the muscle bands of the atria and the ventricles are wrapped up in a network of slender nerve trunks from which delicate plexuses are formed around individual muscle fasciculi and more delicate ones around individual muscle cells. Throughout the myocardium they frequently found delicate, tortuous, varicose, nerve fibrils lying on the individual cells. In good preparations they observed the abundance of nerve fibers within the myocardium and are inclined to agree with those who think that every muscle fiber within the heart is supplied with motor nerve endings.

They conclude with the statement that, until it is proved that the nerve cells within the heart do not originate the cardiac impulse and that the impulse is not carried by the fibers of these cells to the individual units of the myocardium, it is folly to develop theory upon theory to explain impulse formation and conduction on the basis of a nonexistent muscular conduction system.

BERNSTEIN

Sahn, S. H., Leichtling, M., and Bass, H. E.: The Significance of Pleural Effusion in Patients Past the Age of Fifty. New England J. Med. **246:** 927 (June), 1952.

The results of study of 103 patients past the age of 50 with pleural effusion are reported. These patients were observed in two hospitals which do not admit cases of known tuberculosis. Diagnosis was established by thoracocentesis, bronchoscopy or lymph node biopsy or postmortem examination in 70 patients and by presumptive evidence in the remaining 33 patients. Carcinoma was found in 43 per cent, congestive heart failure in 35 per cent. Tuberculosis was present in only one patient. Other causes included pneumonia, pulmonary infarction, lymphoblastoma, cirrhosis, nephrosis, hepatitis, bronchiectasis and trauma. When trauma and pulmonary infarction could be excluded, hemorrhagic pleural effusion was invariably associated with neoplastic disease. Malignant cells were found in 33 per cent of the cases with neoplastic disorders in whom thoracocenteses were done.

ROSENBAUM

BOOK REVIEWS

The Pathogenesis and Treatment of Thrombosis. With a Clinical and Laboratory Guide to Anticoagulant Therapy. *Irving S. Wright, M.D.* Modern Medical Monographs, No. 1. New York, Grune & Stratton, 1952. 86 pages, 27 figures. $3.00.

This monograph combines the George E. Brown Memorial Lecture on "The Pathogenesis and Treatment of Thrombosis" by Irving S. Wright with his "Clinical and Laboratory Guide to Anticoagulant Therapy." The lecture was delivered before the Twenty-fourth Annual Scientific Session of the American Heart Association, Atlantic City, N. J., June 8, 1951, and has been previously published in the February 1952, issue of Circulation. The material presented describes the basic research on blood coagulation. There is included a review of the clinical conditions which involve intravascular clotting and the author's views of the indications and technics for their treatment with the various anticoagulants presently available.

There is great need for this volume which brings as nearly up-to-date as a text may the essential facts and references bearing on this broad, complex, and somewhat controversial subject. Its recorded contents will be appreciated by both physicians and surgeons since the thrombotic processes are of singular importance in the fields of both. Those who may not agree with all the author's recommendations regarding the anticoagulant drugs might well consider the probability that few physicians indeed are as well qualified by intense study and wide experience as is Dr. Wright either to employ these drugs or to outline recommendations concerning them to others. An open mind should be kept until further reports and experience succeed in deciding more certainly some of the moot points.

The text makes it clear that anticoagulants must in each case be managed by a physician experienced in their use who is willing to observe the meticulous care necessary to insure successful therapeutic effect and to avoid hazard to the patient.

The material in the "Clinical and Laboratory Guide to Anticoagulant Therapy" in clearly set forth and brief. Included are excellent descriptions of the methods of laboratory control. It would appear desirable to have included a description of Owren's method of determining the prothrombin time, which has a number of adherents.

To date this monograph is an authoritative, brief presentation of the entire subject; and should serve as an excellent base for understanding the rapidly accumulating literature on the problem from many investigators in different parts of the world.

F. JANNEY SMITH

A Symposium on Essential Hypertension: An Epidemiologic Approach to the Elucidation of its Natural History in Man. Commonwealth of Massachusetts (Recess Commission on Hypertension). Wright and Potter Printing Company Boston, 1951. 373 pages, 70 illustrations, 41 tables, 11 charts, bibliography and index. $3.95.

This volume, a state document of the Commonwealth of Massachusetts, reports appraisals of the problem of hypertension given by American experts in Boston, Massachusetts, Feb. 1–3, 1951. The symposium was sponsored jointly by the Recess Commission on Hypertension of the Massachusetts State Legislature, the School of Public Health and the Bureau of Applied Social Research of Columbia University. In 1949, at the request of the Commission, the latter groups together had undertaken a review of the literature on hypertension available since 1920. This comprehensive bibliography and index of the world literature on blood pressure was on exhibit at the time of the symposium and has since been published separately.

During the three days of the symposium, the participants discussed every field and every approach to the elucidation of the natural history of essential hypertension in man. The presentation included a critical review of the literature dealing with the extent of hypertension; a definition of hypertensive disease; criteria for assessing significant deviations from normal blood pressure; the natural course of essential hypertension; causes of essential hypertension as elucidated by clinical physiologic, anatomicopathologic and experimental animal studies; review of evidence indicating that essential hypertension is not a single disease entity; role of biochemical substances, injury, infection, pregnancy, physical and occupational environment, socio-economic levels, patterns of living, stress and psychogenic influences as initiating and sustaining factors in essential hypertension. The importance of heredity was emphasized and an attempt was made to evaluate methods of identifying and quantitating a hyperreactive response of the cardiovascular system. There was also a discussion of the importance of the sympathetic nervous system in blood pressure regulation as well as the results of sympathectomy in patients grouped as to their different probable life expectancies.

In the final session, a review panel (Clark, Evelyn, Grollman, Hines, Page, Perera, Smithwick, Van Slyke and Wilkins) appraised the state of current knowledge as it was reflected in the material outlined above and adopted a proposal for large scale community research in the epidemiology of essential hypertension in man. The closing remarks by the Commissioner of Public Health of Massachusetts were on "The contribution of organized public health to the solution of the problems outlined by the symposium."

The approach of the participants in the symposium was to indicate the unknown in the field. For this reason alone the volume is worth reading by all interested in the attempt to better understand this complex affliction of man. Historically the volume may well be of great significance. For the first time in the history of studies of the clinical problem of hypertension, the technics of another medical discipline, epidemiology, are being applied in the attempt to define the gaps in our knowledge. Ultimately a hypothesis will be advanced which can be tested in a representative population, including the well and the sick, hypertensive and nonhypertensive.

The methods of epidemiology have been conspicuously successful in making important medical discoveries and contributing to a program of prevention and control long before specific causative agents were identified (smallpox, rabies, endemic goiter, mottled enamel). If the resources of this science are turned to the problem of human hypertension, the outlook may or may not be better.

JOSEPH H. HAFKENSCHIEL

Kreislaufuntersuchungen am Menschen mit fortlaufend registrierenden Methoden. *K. Matthes.* Stuttgart, Georg Thieme Verlag, 1951. 326 pages, 205 figures, 10 tables. 48 DM.

The monograph is based on the large experimental material of the author, but the results are discussed against the background of a quite comprehensive literature. During the past 15 years, the author has developed ingenious methods for continuous recording of arterial oxygen saturation (instrument similar to Millikan's oximeter), photoelectric plethysmography (applied to finger or earlobe), blood pressure (recorded from the finger by means of a photoelectric relay), pulse rate (using a similar photoelectric relay in combination with recording of the charge of an electric condensor), and respiration. While the author is aware that direct arterial blood pressure recording is more accurate, his procedure has the advantage of easier and wider applicability. In this system, up to nine different functions can be continuously recorded. However, in many physiologic situations adequate information about the circulatory mechanism involved can be obtained from three or four functions. With this in mind, the author developed a very compact device with three compartments for three fingers for the simultaneous recording of the pulse rate, blood pressure, arterial oxygen saturation and photoplethysmogram, while the skin temperature is recorded from the thumb.

These methods are applied to the study of circulatory regulations in various normal and abnormal situations (different phases of respiration, breath holding, pressure breathing, hyperventilation, Valsalva experiment, peripheral ischemia, heat and cold application, carotid sinus reflexes, carbon dioxide inhalation, anoxia, and muscular work). Especially detailed is the study of the Cheyne-Stokes type of respiration. A large part of the book (about 90 pages) is devoted to the effect of various drugs.

The large experience of the author is reflected in an authoritative presentation and discussion of the material, which has its lights and its shadows. For the American reader, the condensation of a large, important material is most welcome, the more so as the work which extended through the war and postwar period, is not easily accessible. There is much interesting detail which cannot be discussed in the limited space of this review. The author relies on experience rather than on a quantitative evaluation of the results. The experimental data are, as a rule, presented as typical, but no data are given to show how representative they are. This seems to be especially important for autonomic circulatory regulations, where considerable inter- and intraindividual variability should be expected. Some pertinent information (for instance heart catheterization) is not sufficiently considered. As a whole, however, the book is a valuable source of information for all interested in the wide and intriguing field of circulatory regulations. Publisher and author should be commended for the high quality of illustrations.

ERNST SIMONSON

Rheumatic Fever: A Symposium held at The University of Minnesota on November 29, 30 and December 1, 1951, under the sponsorship of the Minnesota Heart Association. *Edited by Lewis Thomas.* Minneapolis, University of Minnesota Press, 1952. 349 pages, 55 figures, 58 tables. $10.00.

In the great majority of diseases under investigation today the general type of disturbance of the tissues is sufficiently well understood to suggest a direction for research on the mechanism and factors involved in the disease. In the case of rheumatic fever, however, the type of disturbance of the tissue involved is not understood even in the broadest sense. The one probable factor in the etiology of this disease which is agreed upon by most investigators in the field is in fact not a mechanism at all, but an association—that with foregoing infection of the tissues by the hemolytic streptococcus. As to the

means by which this infection leads to the changes found in rheumatic fever—assuming that this association is, indeed, of primary etiologic importance—this might involve a bacterial hypersensitivity or a generalized Arthus or Shwartzman-type reaction to some antigen of the hemolytic streptococcus, perhaps an antigen altered by the growth of the streptococci in the tissues of the host, or a metabolic disturbance of mesodermal tissues by some product of the streptococci, etc.

Under these circumstances a symposium on various aspects of rheumatic fever by a number of investigators active in that field and related ones, such as that held under the auspices of the Minnesota Heart Association last November, is a particularly useful undertaking, as is the volume reviewed here, which is a report of that symposium. Twenty-three participants are involved, and their papers, as well as the discussion which followed them, are presented in full, together with charts, figures and bibliographies of the respective papers. There is a definite emphasis on the hemolytic streptococcus in the areas involving etiology and pathogenesis, and this reflects the general current concentration of effort in this field. The factors involved in the reaction of the host tissues are considered in the areas of the natural history of the disease, in a paper on epidemiology, and in experimental pathogenesis, in several papers describing efforts to reproduce rheumatic-like lesions in lower animals. There are a few papers on subjects which seem to be somewhat removed from the focal point of the symposium, but in general the breadth of range of subjects reported here reflects the wide area over which the etiology of rheumatic fever is being sought.

This volume will be very useful to workers on rheumatic fever, and to those who are interested in the scope of current research in this disease. Symposia by active workers constitute a distinct contribution to areas of research, and one hopes, particularly in so troubled a field as that of rheumatic fever research, that a symposium of this sort will be repeated in the future at some appropriate interval of time.

T. N. HARRIS

Lehrbuch der Röntgenologischen Differentialdiagnostik. I. Erkrankungen der Brustorgane, ed. 3. *Werner Teschendorf.* Stuttgart, Georg Thieme Verlag, 1952. 954 pages, 1030 illustrations. 129 DM.

Two years ago this reviewer reported on the cardiac aspects of a previous edition (1950), on the whole unfavorably. Essentially the faults complained of were that it was not up to date, that newer technics such as angiocardiography and electrokymography were hardly mentioned.

In the present edition these faults have been rectified. There is an eight-page section on angiocardiography and, in addition, numerous references to current work in this field, and illustrations of its use in patent ductus arteriosus, auricular and ventricular septal defects, tetralogy of Fallot, persistent truncus arteriosus, tricuspid stenosis, and transposition of the aorta. The method is sparsely used in the differential diagnosis of mediastinal lesions or where the diagnosis of aortic aneurysm may be in question, situations in which the method has proven to be outstandingly useful.

Eight pages are also devoted to electrokymography, and the current literature and illustrations are on the whole adequate and timely. The book abounds with illustrations of slit-kymography, and from these many assumptions are made, some of which are questionable.

On the other hand the author had introduced us to pneumomediastinography, a technic rarely used in this country. He has expanded greatly on clinical aspects and electrocardiograms where these could supplement our understanding of the disease processes.

The role of a reviewer is similar to that of the literary or theatrical critic. The former edition was reviewed unfavorably, but constructively. In rectifying some of the outstanding omissions, and in amplifying some of the other aspects, the book has assumed many useful aspects, of particular value to those readers of this journal abroad to whom command of the German language and metaphysical concepts are less alien than to most of us here.

JOHN B. SCHWEDEL

Clinical Progress in Cardiovascular Disease. *Edited by Herrman L. Blumgart, M.D.* (Modern Medical Monographs, No. 2.) New York, Grune & Stratton, 1952. 143 pages, 9 figures, 7 tables. $4.50.

This small volume consists of a collection of five articles published in CIRCULATION in the section entitled "Clinical Progress in Cardiovascular Diseases," edited by Dr. Herrman Blumgart.

The symposium on "Atherosclerosis," edited by Dr. Edgar V. Allen, with Dr. Louis N. Katz, Dr. Ancel Keys and Dr. John W. Gofman participating, is comprehensive and yet crystallized sufficiently to afford the reader data with which to formulate his own opinions as to the etiology and pathogenesis of the condition with consideration of the possible effectiveness of therapy. The expressed belief of Dr. Allen that this symposium constitutes the most important published work on atherosclerosis in medical history, seems well founded.

The article by Dr. Clarence E. de la Chapelle and Dr. O. Alan Rose, entitled "The Management of Acute Cardiac Emergencies," is an excellent and complete review of specific therapeutic measures developed as the result of a great experience and knowledge of able physicians and talented teachers.

The section entitled "Surgery for Mitral Stenosis: A Review of Progress," by Dr. Edward F. Bland, represents an interesting historical review of the attempts made to develop a surgical treatment of

mitral stenosis. Emphasis is given the recently developed direct operation of mitral commissurotomy. A highly conservative attitude regarding the clinical indications and contraindications, is clearly expressed.

Dr. A. Carlton Ernstene's article entitled "The Management of Cardiac Patients in Relation to Surgery" is detailed, with practical treatment of the subject which offers considerable information and encouragement to the internist and surgeon who thoroughly study their patients and are vigilant before and after surgery.

In his section, Dr. Mark D. Altschule describes in detail the effect of emotion upon the various physiologic reactions of individuals with normal circulatory systems as well as those with clinical disorders. He emphasizes that the physician will have a better understanding of symptoms of patients referable to this system, if these reactions are borne in mind. It is refreshing and enlightening to have the comments of a physiologist upon emotional reactions, rather than the customary description by those trained in psychosomatics.

The purpose of the collection of essays, to provide a critical appraisal of significant current problems in the cardiovascular field, is fulfilled. The subjects are well chosen, interestingly presented, and certainly should prove helpful to any internist or general practitioner.

ROBERT L. KING

Electrocardiographic Studies in Normal Infants and Children. *Robert F. Ziegler.* Springfield, Ill., Charles C Thomas, 1951. 207 pages, 297 illustrations, 33 tables. $10.50.

In recent years there has arisen an increasing demand for a more accurate evaluation of the electrocardiogram in children. Unfortunately the lack of adequate standards in normal infants and children offered the greatest obstacle. To fill in this gap in knowledge is Dr. Ziegler's objective in his book.

This study was based on electrocardiograms taken on two series of normal infants and children ranging from birth to 16 years of age. The first series consisted of 250 children with unipolar and bipolar extremity leads. The second series of 300 children had complete electrocardiograms both from the limbs and the six precordial locations. The data were analyzed according to the following age distribution: 0 to 24 hours, 1 day to 1 week, 1 week to 1 month, 1 to 3 months, 3 to 6 months, 6 months to 1 year, 1 to 3 years, 3 to 5 years, 5 to 8 years, 8 to 12 years, and 12 to 16 years. Analyses of the tracings included the cardiac mechanism, the various component waves and time intervals, the electrical axis, and the ventricular gradient. Following these chapters, the author presented another entire chapter in the form of an atlas of representative electrocardiograms at various ages. Finally the data were reassembled in a lengthy appendix showing the statistical analyses and distribution curves for each individual item studied.

In this book one sees the striking differences between the electrocardiograms of normal infants and children and those of normal adults, as well as the progression of changes that normally occur throughout infancy and childhood.

Unlike most previous studies based only on bipolar electrocardiograms, Dr. Ziegler presents data from unipolar tracings. To this reviewer, these unipolar data constitute the most important contribution offered by Dr. Ziegler's studies. The prominence of the R wave in the right precordial leads in the younger age groups, the rarity of the Q wave in V_1 (less than 0.5 per cent) even in the newborn infants, the peculiar progression of the T-wave configuration in the chest leads from the infantile to the adult pattern, the greater voltages of the various individual deflections in the precordial tracings, the dominance and greater amplitude of the R wave in aV_R—these are among the most significant distinctive features presented in this book as differentiating the normal standards in infants and children from those of adults.

This book is profusely illustrated with excellent electrocardiograms, a fact that is especially to be commended because of the difficulties that must necessarily be encountered in the taking of the electrocardiograms in newborn and very young infants. The discussions are clearly presented and well illustrated by numerous diagrams and charts. The available literature on the subject, including a number of still unpublished papers of the author, is well covered in every chapter. The printing, as well as the reproduction of the tracings, is excellent.

This reviewer wonders whether the author may not have divided his clinical material too finely according to age distribution and whether some of the age groups could perhaps have been combined. Having fewer age groups would obviously simplify the entire subject and make the data more easily remembered and applied. Overlapping of data in several age groups suggests that such simplification might have been possible. Rather than a purely empiric age-grouping as the book suggests, it would seem that the electrocardiographic features themselves could be assembled in fewer age groups.

This observation aside, the reviewer considers Dr. Ziegler's monograph as one that is as timely as it is important, a contribution hitherto awaited and now finally made available. It furnishes to both the cardiologist and to the pediatrician knowledge on the subject never before so well assembled and analyzed. Considering the increasing application of the electrocardiogram in the younger ages, this book will become a vital reference in this important field.

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RESEARCH AWARDS

The Board of Directors, upon recommendation of the Research Committee of the Scientific Council, has approved fifty-one awards to individual investigators totaling $285,400 for the fiscal year 1953–54. These include the continuation for the third year of a Career Investigator, the continuation of fourteen Established Investigators, six new Established Investigators, the renewal of nine Research Fellows, and twenty-five new Research Fellows.

The awards were made as follows:

Career Investigator

Lorber, Victor, the study of myocardial metabolism, especially fatty acid and ketone body metabolism; the study of trace constituents of the myocardium; University of Minnesota Medical School, Minneapolis.

Continued Established Investigators

Aikawa, Jerry Kazuo, immunophysiology, University of Colorado School of Medicine, Denver.

Bloch, Edward M., a study of the living microscopic blood flow, and vessel walls in patients and experimental animals with thromboembolic phenomena, Western Reserve University, Cleveland.

Edelman, Isidore Samuel, body water and electrolytes studied with tracers, University of California School of Medicine, San Francisco.

Elkinton, J. Russell, cardiovascular physiology, University of Pennsylvania, Philadelphia.

Fishman, Alfred P., cardiodynamic and renal interplay in the production of congestive heart failure, Mount Sinai Hospital, New York.

Gergely, John, energetics and contractile proteins of heart muscle, Massachusetts General Hospital, Boston.

Heller, John H., metabolic and endocrine basis of hypertension and arteriosclerosis, Yale University, New Haven.

Kuhns, William Joseph, immunological and immunochemical studies in rheumatic fever, Rockefeller Institute Hospital, New York City.

Merrill, John P., the further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, Peter Bent Brigham Hospital, Boston.

Mommaerts, Wilfried F. H. M., biochemistry of muscular contraction, Duke University, Durham, N. C.

Peterson, Lysle Henry, volume pressure, "distensibility" of intact veins, arterial circulation with view to calculating stroke volume, integration of peripheral c-v-reflexes, University of Pennsylvania, Philadelphia.

Stamler, Jeremiah, experimental atherosclerosis; experimental hypertension, renal function in edema formation, Michael Reese Hospital, Chicago.

Stefanini, Mario, establishment of "profile" of tests for diagnosis of thrombotic tendency; relation of the endocrine system to the blood coagulation mechanism and the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin in the treatment of thromboembolism, New England Center Hospital, Boston.

Tobian, Louis, Jr., the relation of steroids and sodium to hypertension; the role of steroids and sodium to hypertension; the role of steroid intoxication in toxemia of pregnancy; the role of emulsifying forces in plasma in pregnancy; the role of emulsifying forces in plasma in atherosclerosis, Harvard Medical School, Boston.

New Established Investigators

Cohn, Mildred, mechanisms of phosphorylation and phosphate transfer reactions, Washington University School of Medicine, St. Louis, Mo.

Curran, George Lally, the metabolic aspects of cardiovascular disease with particular reference to lipid metabolism, Research Laboratories, The Mary Imogene Bassett Hospital, Cooperstown, N. Y.

Grisolia, Santiago, enzymatic patterns of nitrogen metabolism in heart muscle. University of Wisconsin, Madison.

Lepeschkin, Eugene, electro-physiological interpretation of the normal and pathological ventricular complex of the electrocardiogram. University of Vermont, Burlington.

Metcalfe, James, changes in the maternal circulation during pregnancy and labor, Boston Lying-in Hospital, Boston.

Plaut, Gerhard, W. E., pathways and compounds of intermediary metabolism with particular regard to the properties of heart muscle, University of Wisconsin, Madison.

Renewal Research Fellows

Cavert, Henry Mead, metabolism and permeability of heart tissue investigated with isotopic techniques,

under Victor Lorber, University of Minnesota, Minneapolis.

Cortier, Claude, neuro-endocrinological factors of cardiovascular disease, under G. W. Harris, Maudsley Hospital, London.

Harb, Solomon, physiology and pharmacology of isolated mammalian heart muscle, under McKeen Cattell, Cornell University Medical College, New York City.

Kleinerman, Jerome Irving, study of myocardial nutrition or effective circulation by the Radiosodium clearance of Na^{24} ($Sodium^{24}$), under Thomas D. Kinney and Alan Moritz, Western Reserve University, Cleveland.

Osborn, John J., continuation of experimental studies on methods for the interruption of the cardiac and pulmonary circulations by refrigeration and with a new type of oxygenator, under L. Emmett Holt, New York University, New York City.

McIntosh, Henry Dean, receptor areas in the control of blood volume and electrolytes in man, under James V. Warren, Duke University School of Medicine, Durham, N. C.

Mateer, Frank Marion, 1. cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technique; 2. ballistocardiographic studies in the normal and abnormal subjects, under T. S. Danowski, University of Pittsburgh.

Nelson, Clifford Vincent, studies on the electrical field of the heart, under Samson Wright, Middlesex Hospital, London.

Rowe, George Giles, evaluation of cerebral, coronary, and renal blood flow in hypertension, under Charles W. Crumpton, University of Wisconsin, Madison.

New Research Fellowships

Abelmann, Walter H., cardiovascular dynamics in liver disease and other metabolic disorders, their determinants, under Laurence B. Ellis, Thorndike Memorial Laboratory, Boston.

Baird, Catherine Dorothy, study of the effects of nutritional deficiencies during gestation on the cardiovascular system of the offspring, under Herbert M. Evans, University of California, San Francisco.

Balchum, Oscar J., pulmonary-circulatory hemodynamics in acquired and congenital heart disease, under S. Gilbert Blound, University of Colorado, Denver.

Briller, Stanley Arthur, energetics of the myocardium under Charles E. Kossmann, New York University, New York City.

Camara, Augusto, studies of changes in the volume, concentration and composition of the extracellular fluid in patients with heart disease with edema and with oliguria or anuria, with special reference to acid-base balance, under Ferdinand R. Schemm, Spencer Memorial Hospital, Great Falls, Mont.

Conrad, Loyal Lee, a study of the plasma artilipemia factor in atherosclerosis, under Robert H. Furman, Oklahoma Medical Research Institute, Oklahoma City.

Cugell, David Wolf, cardiopulmonary hemodynamics, under Richard Riley, Johns Hopkins Hospital, Baltimore.

D'Angelo, George Joseph, study of effects of intervals of ischemia and chronic ischemia following arterial obstruction. Determination of critical levels for survival of tissues and effects of several therapeutic agents and of infusion of solutions beyond the point of obstruction, under Keith S. Grimson, Duke University, Durham, N. C.

Dontas, Anastasius, S., electrical study of ganglionic and adrenic blocking agents. Dynamics of prolonged altered homeostasis in the cardiovascular system, under M. H. Seevers, University of Michigan, Ann Arbor.

Englard, Sasha, the mechanism of riboflavin biosynthesis, under Sidney P. Colowick, McCollum Pratt Institute, Baltimore.

Freeman, Oscar W., Jr., (1) study of edema formation in congestive heart failure, cirrhosis and other disease states; (2) electrolytic effects on the myocardium and role in cardiovascular renal disease; (3) treatment of glomerulonephritis and nephrosis with ACTH, under Arthur J. Merrill, Emory University, Atlanta, Ga.

Hamrick, Ladd Watts, Jr., continuation of studies on splanchnic blood flow and metabolism, under J. D. Myers, Duke University, Durham, N. C.

Ling, Johnson, S. L., cardiovascular pharmacology, under John C. Krantz, University of Maryland, Baltimore.

Mathews, Martin B., the physical chemistry of the acid mucopolysaccarides of connective tissue and their protein complexes, under Lowell T. Coggeshall, University of Chicago.

Neill, Catherine Annie, the development of conducting tissue in the human embryo, under Helen B. Taussig, Harriet Lane Home, Baltimore.

Rakita, Louis, the nature of the electrocardiographic changes in coronary occlusion, under Myron Prinzmetal, Cedars of Lebanon Hospital, Los Angeles.

Rapaport, Elliot, circulatory dynamics of mitral insufficiency and their clinical correlations, under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Skelton, Floyd Reginald, the role of certain androgenic steroids in the production of experimental hypertension and cardiovascular-renal disease, under Robert E. Stowell, University of Kansas, Kansas City, Kansas.

Topper, Yale J., the chemistry and enzymology of co-enzyme A, under Fritz Lipmann, Harvard Medical School, Boston.

Von Korff, Richard Walier, studies in intermediary metabolism, under Lewis Thomas, University of Minnesota, Minneapolis.

Warner, Homer Richards, relationship of heart rate to cardiac output in normal subjects and in patients with heart disease, studied with the pressure pulse method, under Hans Hecht, University of Utah, Salt Lake City.

SCIENTIFIC COUNCIL

The Scientific Council of the American Heart Association is completing the process of reorganization which was begun to allow for broader participation by physicians and scientists in the scientific affairs of the Association. The new Rules and Regulations, recently approved by the Board, provide that any physician who is a member of the Association or an affiliate may become a member of the Scientific Council upon application.

Scientists and other professional persons who are not physicians may become members through election to a Section of the Scientific Council by virtue of their activity in the Section's particular field of interest, and provided they become members of the Association or one of its affiliates. It is urged that at the time of application for membership to the Scientific Council physicians also indicate in writing to the Medical Director the Section of their choice. Three new Sections of the Council, one on Clinical Cardiology, one on Vascular Surgery, and a Section on Basic Sciences, are being organized. The three continuing divisions of the Council are the Sections on Circulation and on High Blood Pressure Research, and the Council on Rheumatic Fever and Congenital Heart Disease.

NEW AFFILIATE

The Utah Heart Association has become the fifty-ninth direct affiliate of the American Heart Association. There are 351 chapters under the jurisdiction of the state and regional affiliates.

These Heart Associations have a total of approximately 14,800 voting members, of whom 7,800 are physicians, and 7,000 are laymen.

NEW STAFF CONSULTANT

Frederick A. Whitehouse, Ed.D., formerly director of Vocational Rehabilitation and Education of the Institute for the Crippled and Disabled has joined the staff of the Community Service and Education Division of the American Heart Association as a consultant on employment problems of the cardiac. This position was recently created because of the rapid growth of "Cardiac-in-Industry" programs in heart associations throughout the country.

ANNUAL REPORT

The Association's 1952 Annual Report has been published and copies are available on request.

MEETINGS

May 15–16: Annual Meeting, Section on High Blood Pressure Research, American Heart Association, Cleveland, Ohio. George Wakerlin, M.D., Chairman, Program Committee, 1853 W. Polk Street, Chicago 12, Ill.

May 28–31: 19th Annual Meeting, American College of Chest Surgeons, Hotel New Yorker, N.Y.C. Executive Director, Murray Kornfeld, American College of Chest Surgeons, 112 East Chestnut Street, Chicago 11, Ill.

June 1–5: Annual Session, American Medical Association, N.Y.C. Secretary, George F. Lull, M.D., 535 N. Dearborn St., Chicago 10, Ill.

June 7–9: American College of Cardiology, 2nd annual convention, Hotel Statler, Washington, D.C., Secretary, Philip Reichert, M.D., 480 Park Avenue, N. Y. 22, N. Y.

September 18–20: Congress of the International Society of Angiology, Lisbon, Portugal. Secretary, Dr. Henry Haimovici, 105 East 90th St., N. Y. 28, N. Y., U. S. A.